DEVELOPMENT OF FAST DISSOLVING TABLETS OF TORSEMIDE

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CERTIFICATE

بسم الله الرحمن الرحيم
In the Name of Allāh, the Most Gracious, the Most Merciful

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CERTIFICATE

This is to certify that the dissertation entitled **"Development of Fast Dissolving Tablets of Torsemide"** submitted by **Mrs.S.Ponnammal Asmi (M. Pharm II year)**, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by her, under my guidance and supervision in the Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-20 during the academic year 2013 – 2014.

This dissertation is forwarded to the Controller of Examinations, The Tamilnadu Dr. M.G.R. Medical University, Chennai-32.

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CONTENTS

CONTENTS

CHAPTER I

INTRODUCTION

CHAPTER - I

INTRODUCTION

ORAL MUCOSAL DRUG DELIVERY SYSTEM

Oral mucosal drug delivery system is widely applicable as novel site for administration of drug for immediate and controlled release action by preventing first pass metabolism and enzymatic degradation due to GI microbial flora. It is subdivided into buccal and sublingual in which buccal cavity is widely applicable for drug administration through mucosa in case of sublingual route mostly useful for fastest onset of action as in the case of angina pectoris.

The buccal mucosa lines the inner cheek and buccal formulations are placed in the mouth between the upper gingival (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligo nucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery. (Radha bhati *et al*., 2012)

Advantages

- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be continued.
- Increased easy of administration.

- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Limitations

- For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of food stuffs may lead to the requirement for frequent dosing.
- The non uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective level.
- For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue. (Radha bhati *et al*., 2012).

OVERVIEW OF ORAL MUCOSA

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The top quarter to one third of the oral mucosa is made up of closely compacted epithelial cells. The oral mucosa also contains many sensory receptors including the receptors of the tongue.

Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (upper surface of the mouth) and the gingival (gums). The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial

cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and sub mucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces which are both keratinized and some non-keratinized. (Srivastava saurakh *et al*., 2012)

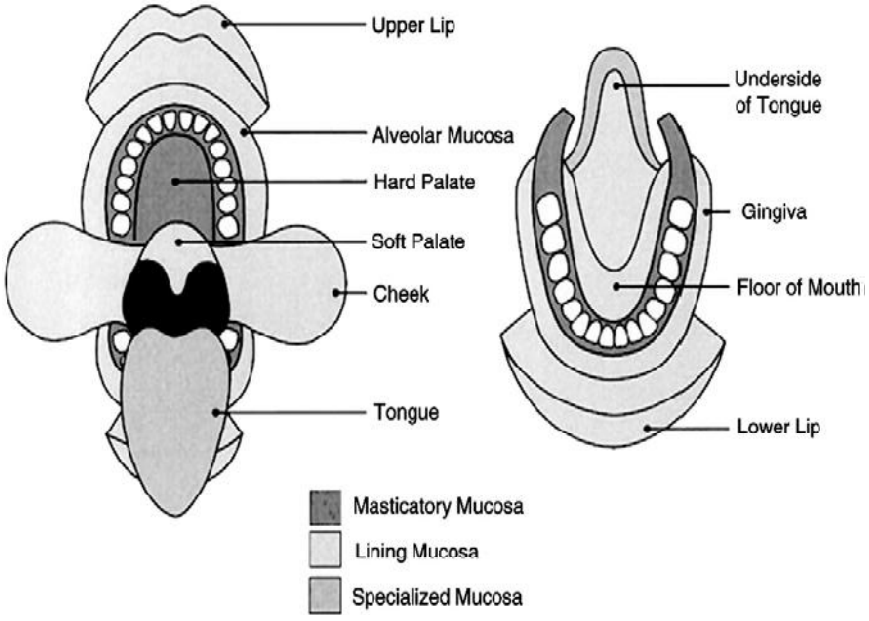


Figure 1: Schematic representation of the different linings of mucosa in mouth

FAST DISSOLVING TABLETS

Dysphagia or difficulty in swallowing is common among all age groups. Dysphagia is common in about 35% of the general population, as well as additional 30-40% of elderly institutionalized patients and 18-22% of all persons in long term care facilities. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc. Parkinsonism, motion sickness, unconsciousness, elderly patients, children, mentally disabled persons, unavailability of water. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms.

The tablets is the most widely used dosage form existing today because of its convenience in terms of self administration, compactness and ease in manufacture. However, geriatric, pediatric and mentally ill patients experiences difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery system known as mouth dissolving / disintegrating tablets (MDTs) rapimelts are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and orally disintegrating tablets. However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as rapimelts. Recently, European Pharmacopoeia has used the terms orodispersible tablet for tablets that disperses readily and within 3min in mouth before swallowing.

Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. Their growing importance was underlined recently when European pharmacopoeia adopted the term "orodispersibles tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. The bioavailability of some drugs maybe increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. (Mangal mohit *et al*., 2012)

Advantages

- Administration without water.
- Convenience of administration.
- Accurate dosing as compare to liquids.
- Easy portability.
- Ideal for pediatrics and geriatric patients.
- Rapid dissolution/absorption of the drug, which may produce rapid onset of action (Brahma reddy D.R. *et al*., 2011).

Disadvantages

- Fast dissolving tablet is hygroscopic in nature so must keep in dry place.
- Fast dissolving tablet requires special packaging for properly stabilization and safety of stable product (Ashish.P. et al., 2011).

Limitations

- The tablets usually have insufficient mechanical strength. Hence careful handling is required.
- Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500mg of the drug.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly (Mangal mohit *et al*., 2012 and Alok kumar gupta *et al.,* 2011).

Desired criteria for mouth dissolving drug delivery system

- Mouth dissolving tablet should not require water to swallow, but it should dissolve or disintegrate in the mouth within matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Convenience of administration and accurate dosing as compared to liquids (Raja shree panigrahi *et al*., 2010).

Technologies used for manufacturing of MDTs

1. Lyophilization or freeze drying

A process in which water is sublimed from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

2. Molding

In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Molded tablets are very less compact than compressed tablets. These posses porous structure that enhances dissolution (Rakesh kumar bhasin *et al,* 2011).

3. Cotton candy process

This process is named as it utilizes a unique spinning mechanism to produce floss like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MDTs (Alok kumar gupta *et* al., 2011).

4. Spray drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and in acidic material(eg. citric acid) and or alkali material (eg. Sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20seconds when immersed in an aqueous medium (Rakesh kumar bhasin *et* al., 2011).

5. Mass extrusion

This technology involves softening the active blend using the solvent mixture of water soluble poly ethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste (Pooja mathur *et al*., 2010).

6. Sublimation

The slow dissolution of the compressed tablet containing even highly water soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (eg. Urea, ammonium carbonate, ammonium bicarbonate, hexa methylene tetramine, camphor etc) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Additionaly, several solvents (eg.

Cyclohexane, benzene) can be also used as pore forming agents (Ashish. P *et al*., 2011).

7. Nanonization

A recently developed nanomelt technology involves reduction in the particle size of drug to nano size by wet milling technique. Surface adsorption of the nanocrystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (upto 200mg of drug per unit).

8. Direct compression

Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production method. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent (Alok kumar gupta *et al*., 2011).

Patented technologies for fast dissolving tablets

- Zydis technology.
- Orasolve technology.
- Durasolv technology.
- Flashdose technology.
- Shearform technology.

- Wowtab technology.
- Flashtab technology.
- Dispersible tablet technology.
- Frosta technology.
- Pharmaburst technology.
- Ora quick technology.
- Quick Dis technology.
- Nano crystal technology.
- Ziplets/ Advatab technology.
- Ceform technology.
- Quick solv technology.
- Lyo technology.

Zydis technology

This technology involves softening the active blend using the solvent mixture of water soluble poly ethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Orosolv technology

Orosolv technology has been developed by "CIMA" labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force inorder to

minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system (Srivastava saurabh *et* al., 2012 and Nishtha tiwari *et* al., 2012).

Durosolv technology

Durosolv is the patented technology of "CIMA" labs. The tablets made by this technology consist of a drug, fillers and lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durosolv is an appropriate technology for products requiring low amounts of active ingredients (Ashish .P *et* al., 2011 and Rajashree panigrahi *et* al., 2010).

Flashdose technology

Flashdose technology has been patented by "FUISZ" nurofen meltlet, a new form of ibuprofen as melt in mouth tablets, prepared using flashdose technology is the first commercial product launched by "Bioavail Corporation". Flash dose tablets consist of self binding shearform matrix termed as "FLOSS". Shear form matrices are prepared by flash heat processing (Alok kumar gupta *et al*., 2011 and Pooja mathur *et* al., 2010).

Shearform technology

It's based on preparation of floss that is known as shearform matrix, which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, sugar is simultaneous subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal,

flow condition, which permits part of it to move with respect of mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystalised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystalised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients canbe blended with floss before carrying out recrystallisation. The shearform floss, when blended with the coated or uncoated microspheres, is compressed into flash dose or EZ chew tablets (Srivastava saurabh *et* al., 2012).

Wowtab technology

Yamanouchi's WOWTAB^{R} (without water) technology employs a combination of saccharides to produce fast dissolving tablets using conventional granulation , blending, drying and direct compression of tablets. Taste masking is provided by the combination of one or more sugar like excipients or microencapsulation of the active ingredients. These tablets exhibit significant hardness allowing packaging in conventional bottles or blisters.

Flashtab technology

Prographarm laboratories have patented the flashtab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules maybe prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tabletting technology.

Dispersible tablet technology

Lek, Yugoslavia patents this technology. It offers development of MDTs with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration. Disintegrants include starch, modified starches, micro crystalline cellulose, alginic acid, cross linked sodium carboxy methyl cellulose and cyclo dextrins combination of disintegrants improves disintegration of tablets usually less than 1minute.

Frosta technology

This technology patents by akina. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of: porous and plastic material, water penetration enhancer and binder. The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

Pharmaburst technology

SPI pharma, new castle, patents this technology. It utilizes the coprocessed excipients to develop MDTs, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricants followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Oroquick technology

The oraquick ODT formulation utilizes a patented taste masking technology by KV pharmaceutical company, who claims that its taste masking technology ie. Microsphere technology (micromask) has superior mouth feel over taste masking alternatives. The taste masking process doesnot utilize solvents of anykind and therefore leads to faster and superior efficient production. Tablet with significant mechanical strength without distrupting taste masking are obtained after compression. Oraquick claims quick dissolution in matter of seconds with good taste masking. There are no products yet in the market using oraquick technology, but KV pharmaceutical has products, having different classes of drugs such as analgesics, cough and cold, psychotics and anti infective, in developmental stage (Rajashree panigrahi *et* al., 2010).

Quick-dis technology

Lavipharm has invented an ideal intra – oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick –Dis ™, is Lavipharms" proprietary patented technology and is a thin, flexible, and quick dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis ™ film with a thickness of 2mm. the dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2mm.

Nanocrystal technology

This is patented by Elan, King of Prussia. Nano crystal technology includes lyophilization of colloidal dispersions of drug substance and water soluble ingredients filled into blisters pockets.this method avoids manufacturing process such as granulation, blending and tabletting which is more advantages for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

Ziplets/advatab technology

It utilizes water insoluble ingredient combined with one or more effective disintegrants to produce MDT with improved mechanical strength and optimal disintegration time at low compression force.

Ceform technology

This technology involves preparation of microspheres of active drugs. Drug material alone or in combination with other pharmaceutical substance and excipients is placed into a precision engineered rapid spinning machine. The centrifugal force comes into action, which throw the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The microspheres are thus formed are compressed into tablets. As the drugs and excipients both can be processed simultaneously, it create a unique micro environment in which the material can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability.

Quicksolv technology

This technology used two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

Lyo technology

Lyo technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze drying. Non homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered (Srivastava saurabh *et al*., 2012).

Ingredients to be used for fast disintegrating tablet

Important ingredients that are used in the formulation of fast disintegrating tablets should allow quick release of the drug, resulting in faster dissolution. This includes both the active and inactive ingredients excipients balance the properties of the actives in fast disintegrating tablets.

Binders

The choice of a binder is critical in a fast dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Binders keep the composition of these fast dissolving tablets together during the compression stage. The right selection of a binder or combination of

binders is essential to maintain the integrity and stability of the tablet. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as poly ethylene glycol.

Lubricants

Lubrications are used for to reduce the friction during compaction and ejection of tablets in present study magnesium stearate and talc were used as lubricant.(eg) stearic acid, magnesium stearate, poly ethylene glycol, liquid paraffin, magnesium lauryl sulfate (Brahma reddy D.R *et* al., 2011).

Bulking agent

The material contributes functions of a diluents, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentrations of the active in the composition. The recommended bulking agents for this delivery system should be more sugar based such as mannitol, poly dextrose, lactate and starch hydrolysate for higher aqueous solubility and good sensory perception.

Emulsifying agents

Emulsifying agents are important excipients for formulating fast melting tablets, they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast tablet formulation, including alkyl sulfates.

Flavours and sweetners

Flavours are peppermint, aromatic oil, clove oil, anise oil, eucalyptus oil thyme oil, vanilla, citrus oil. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non nutritive sweeteners such as aspartame, sugar alcohols and sucralose (Brahma reddy D.R *et* al., 2011).

Role of superdisintegrants

As days passes, demand for faster disintegrating formulation is increased. So pharmacist needs to formulate disintegrants ie.,super disintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

Mechanism of action of super disintegrants: the tablet breaks to primary particles by one or more of the mechanism listed below

1. By swelling.
2. By capillary action.
3. Due to disintegrating particle/ particle repulsive forces.
4. Due to deformation.
5. Due to release of gases.

1. By swelling

Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

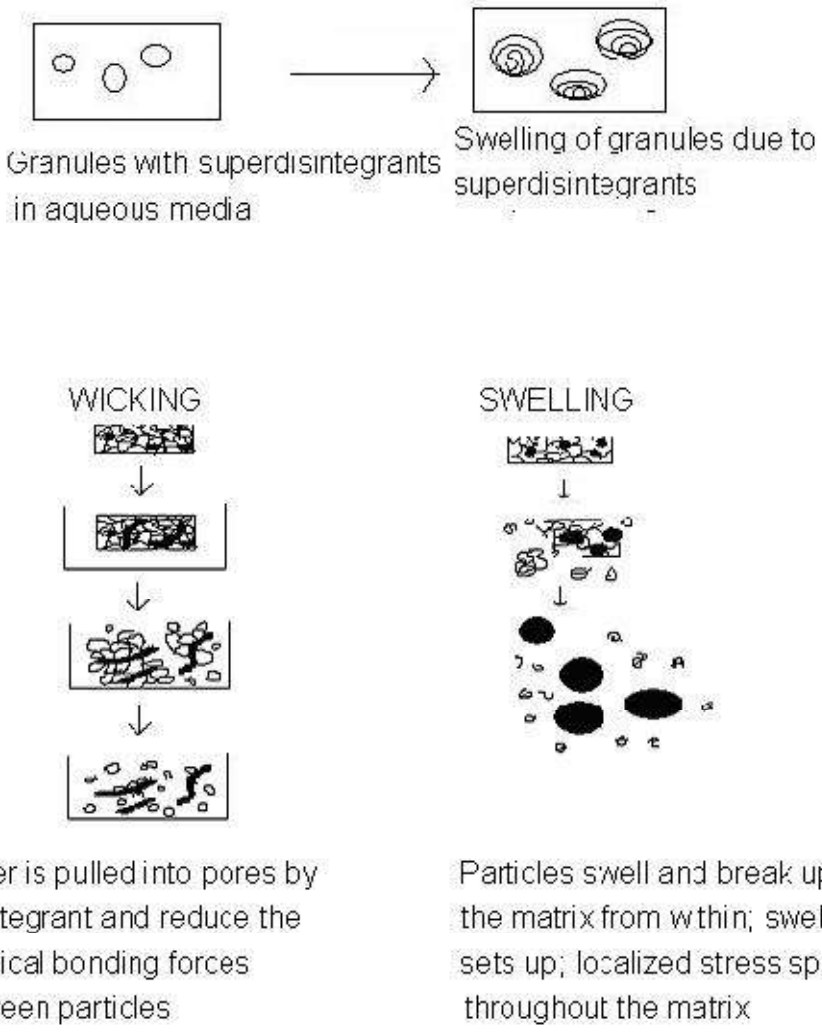


Figure 2: Schematic representation of mechanism of action of super disintegrants by swelling

2. By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air absorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/ excipient and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

3. Due to disintegrating particle/ particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. Due to deformation

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

5. Due to release of gases

Carbondioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid and tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation (Nishtha tiwari *et* al., 2012).

CHAPTER II

LITERATURE REVIEW

CHAPTER – II

LITERATURE REVIEW

Bhingare C.L. et al., 2013, formulated and evaluated mouth dissolving tablets of zolpidem tartrate to improve bioavailability and circumvent the first pass effect by direct compression method using croscarmellose sodium, sodium starch glycolate as superdisintegrants and mannitol, microcrystalline cellulose, dicalcium phosphate as diluents. It could be concluded that mouth dissolving tablets of zolpidem tartrate were successfully formulated to improve the drug release profile.

Kadria A. Elkhodairy et al., 2013, formulated and optimized orodispersible tablets of flutamide by direct compression technique using three different approaches namely; super disintegration, effervescence and sublimation. Different combined approaches were proposed and evaluated to optimize tablet characteristics. Sodium starch glycolate (SSG) was used as super disintegrant. The incorporation of 1:5 solid dispersion of FTM: PEG 6000 instead of the pure drug in the same formulation increased the drug release rate from 73.12 to 96.99% after 15 minutes. This increase in the dissolution rate may be due to the amorphization of the drug during the solid dispersion preparation. The presence of amorphous form of the drug was shown in the IR spectra.

Kamal Saroha et al., 2013, formulated and evaluated fast dissolving tablets of amoxicillin trihydrate using synthetic super disintegrants such as sodium starch glycolate(SSG) and croscarmellose sodium(CCS); microcrystalline cellulose(MCC) as direct compressible diluents by direct compression technique. The study concluded

that 10% CCS showed better disintegrating property and drug release upto 99.78% within 25min than the most widely used synthetic superdisintegrants like SSG.

Manish R.Bhise et al., 2013, formulated and evaluated intra orally fast dissolving tablet of olmesartan medoxomil were prepared by using three different superdisintegrants like crosscarmellose sodium, sodium starch glycolate and crospovidone. The results showed that 8% crosspovidone was found to be an optimized batch.

Mohanthesh A.M.K. et al., 2013, formulated and evaluated mouth dissolving tablets norfloxacin an antibacterial agent using different superdisintegrants like sodium starch glycolate, crosscarmellose sodium (CCS), crospovidone by direct compression technique. The results revealed that the increased proportion of various superdisintegrants were associated with increase in the overall cumulative drug release rate.

Pavan K.Rawat et al., 2013, formulated and evaluated fast dissolving tablets of pioglitazone hydrochloride were prepared by direct compression method using super disintegrants such as croscarmellose, crospovidone, indion 414. The study shows that the dissolution rate of pioglitazone could be enhanced to a great extent by combinations of superdisintegrants by direct compression technique.

Preeti Karwa et al., 2013, developed fast dissolving tablets of losartan potassium were designed using super disintegrant such as kollidon CL-SF in different concentrations by direct compression technique. The result shown that the superdisintegrant disintegrate within few seconds without need of water so as to overcome swallowing difficulties.

Vishakha S.Hastak et al., 2013, formulated and evaluated fast dissolving tablets of gliclazide were prepared using crosscarmellose sodium and sodium starch glycolate as superdisintegrant separately and then in combination by direct compression method. The result were observed that among two superdisintegrants crosscarmellose sodium (5%) showed better result in disintegration time and maximum invitro drug release of 99.89% at the end of 20 minutes.

Anas Bahnassi et al., 2012, formulated and evaluated aceclofenac fast dissolving tablets using foam granulation technique. It is a newer technique that promises better distribution of the granulating system and better properties for the produced tablets. Aceclofenac was selected as the model drug. The poor hydrophilicity of the drug results in variable dissolution rate and poor bioavailability. This study was performed to prepare aceclofenac ODTs using the newer technique and various types of disintegrants, glidants and lubricants. It was concluded that the prepared aceclofenac ODTs by foam granulation technique using selective range of excipients can provide a dosage form with better patient compliance and effective therapy.

Deshmukh.V.N. et al., 2012, developed and evaluated orally disintegrating tablets by direct compression method. Taste masking of ondansetron was carried out by adding trusil lemon lime ASV, peppermint powder as flavouring agent and aspartame as sweetening agent, using croscarmellose sodium, sodium starch glycolate, crospovidone as super disintegrant while the other components were kept constant. Nine formulations f_1-f_9 were prepared by varying the concentration of super disintegrants. The total weight of tablet was kept constant (100mg) and drug content was 4mg. The formulations containing crospovidone (20%, 25%, and 30%) showed lowest disintegration time, wetting time and dispersion time. All the formulations

release more than 80% of drug within 30 minutes which prove it fast dissolving action. Based on dissolution rate superdisintegrants can be ranked as crospovidone > sodium starch glycolate > croscarmellose sodium. Among all the formulated tablets containing 25%crospovidone showed good compressibility, flowability and less friability, it also showed less disintegration, wetting time, dispersion time and percentage cumulative release of drug was 99.47% in 10 minutes. It was concluded that the ideal bitterless orally disintegrating ondansetrons tablet were prepared successfully.

Devendra revanand rane et al., 2012, formulated and evaluated fast dissolving tablets of albendazole with a view to and provide quick onset of action. The study was to formulate fast dissolving tablets of albendazole to achieve a better dissolution rate and further improving bioavailability of the drug. FDTs were prepared by direct compression technique using super disintegrants in different concentrations. The formulation containing 5% w/w super disintegrant crospovidone and 20%w/w micro crystalline cellulose was considered to be the best formulation, which releases up to 99.09% in 40 minutes.

Hasan Mahmud Reza et al., 2012, formulated, designed and evaluated baclofen mouth dissolving tablets. The aim of this study was to prepare mouth dissolving tablets of baclofen using various super disintegrants like kollidon CL-SF, crospovidone, sodium starch glycolate and ludiflash by direct compression method. Among all the formulations tablets containing kollidon CL-SF, sodium starch glycolate and ludiflash showed superior organoleptic properties along with excellent invitro disintegration and drug release pattern as compared to that containing croscarmellose. It could be concluded that mouth dissolving tablets of Baclofen were

prepared successfully using F_1 and F_2 formula as they satisfy the criteria of a mouth dissolving tablet and would be the alternative to the currently available conventional tablets.

Kusum devi et al., 2012, performed in vitro and in vivo evaluation of fast dissolving tablets containing solid dispersion of pioglitazone HCl. Polyvinyl pyrrolidine K30 carrier was selected and solid dispersions were prepared by various methods. The best formulation has shown Tmax of 1 hour which was highly significant ($p > 0.01$) when compared with pure drug and marketed formulation. Therefore, the solid dispersions prepared by kneading method using PVP K30 as hydrophilic carrier can be successfully used for improvement of dissolution of PIO and resulted in faster onset of action as indicated by in vivo studies.

Ravi S. Wanare et al., 2012, formulated and evaluated fast dissolving tablets of azithromycin dihydrate using different super disintegrants. In this study different super disintegrants were used such as sodium starch glycolate, croscarmellose sodium and crospovidone. In all the formulations water was used as binding agent to attain hardness. The prepared fast disintegrating tablets were evaluated. Wetting time of formulation containing sodium starch glycolate was the least and tablets showed much faster disintegration. All the tablets had hardness of 3.1- 5.3 kg/cm^2 and friability was less than 1%. Among all formulations FDT 7 showed least disintegrating time of 21.40 seconds.

Shaikh RG. et al., 2012, designed, optimized and evaluated orally disintegrating tablets of antiemetic drug. The bitter taste of the drug was masked by kyron T 114, (weak cation exchange resin) by ion exchange resin complexation method, which was prepared by the batch technique. The resin ratio and pH was optimized to successfully

formulate the resinate into ODT and it was confirmed by FTIR and DSC study. In preliminary trials, selection of super disintegrants (i.e., crospovidone XL 10, crosscarmellose sodium and sodium starch glycolate) and selection of diluents (i.e., mannitol SD 200, Avicel pH 102, Avicel pH112, starch and pregelatinized starch) were made. The cohesive force of mannitol increases wetting time and disintegration time so drug release was delayed. Results from an evaluation by a panel of ten human volunteers demonstrated that the orally disintegrating tablets prepared by kyron T 114 improved the taste significantly.

Abhishek Jain et al., 2011, formulated and evaluated aceclofenac fast dissolving tablets using superdisintegrants such as croscarmellose sodium, crospovidone, sodium starch glycolate and sodium lauryl sulphate as surfactant by direct compression method. The tablet disintegrated within 18 to 49 seconds and almost 90% of drug was released from all formulations within 15 minutes. Stability studies of the tablets at 40 ± 2/75% ± 5% RH for 3 months showed non significant drug loss. The formulations containing 6% of croscarmellose sodium was found to be the best.

Basawaraj S. Patil et al., 2011, formulated and evaluated fast dissolving tablets of tizanidine HCl by direct compression method. Super disintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone on wetting time, invitro dispersion time and stability parameter has been studied. From this study it was concluded that fast dissolving tablets prepared by direct compression method using different super disintegrants enhanced dissolution to improve bioavailability and effectiveness of tizanidine HCl.

Basawaraj S Patil et al., 2011, formulated and evaluated fast dissolving tablets of granisetron hydrochloride by direct compression technique. Super disintegrants such

as croscarmellose sodium, sodium starch glycolate and crospovidone, on wetting time, invitro dispersion time and stability parameter has been studied. From this study it was concluded that fast dissolving tablets were prepared by direct compression method using different super disintegrants enhanced dissolution to improve bioavailability and effectiveness of granisetron hydrochloride.

Bhanushali Akash K. et al., 2011, formulated and evaluated mouth dissolving tablets of isosorbide mononitrate using crospovidone as super disintegrant. The tablets were prepared by direct compression method. This technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of mouth dissolving tablets. It can be concluded that disintegration and dissolution rate of isosorbide mononitrate can be enhanced to great extent with addition of super disintegrants.

Biswajit Basu et al., 2011, formulated and evaluated fast dissolving tablets of cinnarizine using super disintegrant blends and subliming material. A combination of super disintegrants sodium starch glycolate (SSG) and crosscarmellose sodium (CCS) was used along with camphor as a subliming material. An optimized concentration of camphor was added to aid the porosity of the tablet. A 3^2 full factorial design was applied to investigate the combined effect of two formulation variables: amount of SSG and CCS. In the present study, direct compression was used to prepare the tablets. Camphor was sublimed from the tablet by exposing the tablet to vaccum drier at 60^0C for 12 hours. An optimized tablet formulation (fa) was found to have good hardness of 3.30±0.10 kg/cm^2, wetting time of 42.33±4.04 seconds, DT of 34.67±1.53 seconds, and cumulative drug release of not less than 99% in 16minutes.

Chandrasekhar Patro et al.,2011, formulated and evaluated cetirizine hydrochloride mouth fast dissolving tablets using different concentrations of super disintegrants like crospovidone(CP), croscarmellose sodium(CCS), sodium starch glycolate (SSG).Tablets were prepared by direct compression method and evaluated. The results indicate that formulation prepared with 5% croscarmellose sodium was found to be optimized which provides maximum drug release (99%) and minimum disintegration time (less than 20 sec). Stability studies of optimized formulation revealed that formulation is stable.

Himmat Singh et al., 2011, formulated and evaluated mouth dissolving tablets of carvedilol. The solubility of carvedilol was enhanced with different ratios of PVP by the solvent evaporation method. Invitro release profile of solid dispersion obtained in SGF without enzymes and pH6.8 phosphate buffer indicate that 100% drug release found within 20 minutes. This solid dispersion was directly compressed into tablets using crospovidone, sodium starch glycolate, and croscarmellose sodium and polacrilin potassium in different concentration as a super disintegrant. The prepared tablets containing the solid dispersion of carvedilol were found to have sufficient strength of 2.5-4Kg/cm^{2}which disintegrated in the oral cavity within 21 seconds contain crospovidone (5%) as super disintegrant.

Rashmi dahima et al.,2011, formulated and evaluated aceclofenac mouth dissolving tablets were prepared with two different techniques, wet granulation and direct compression, in which different formulation were prepared with varying concentrations of excipients. The tablets were evaluated for the drug release profile in phosphate buffered saline (PBS) PH7.4. Direct compression batch C_3 gave far better

dissolution than the wet granulation batch F_2, which released only 75.37%drug and C_3 released 89.69%drug in 90 minutes.

Ravikumar Nayek et al., 2011, formulated and evaluated fast dissolving tablets of lornoxicam were prepared using super disintegrants viz; crospovidone, croscarmellose sodium and sodium starch glycolate by direct compression method. The different formulations showed disintegration time between 18 to 75 seconds and drug release showed time between the ranges of 10 to 12 minutes. Among all the formulations, f3 (containing 4% of crospovidone) showed 99% drug release within 12 minutes and disintegration time in 18 seconds. Thus F_3 was considered best among the other formulations. The stability study was conducted as per the ICH guidelines and the optimized formulation (F_3) was found to be stable, with insignificant change in hardness, drug content and disintegration time. Therefore the main objective of the present work is to develop orodispersible tablets of lornoxicam to improve bioavailability, disintegration time, dissolution efficacy and patient compliance.

Sarasija Suresh et al., 2011, formulated, designed and optimized fast dissolving clonazepam tablets by sublimation method with a view to enhance patient compliance. Croscarmellose sodium (2-8% w/w) was used as super disintegrant and camphor (20-40% w/w) was used as subliming agent, to increase the porosity of the tablets, since it helps water to penetrate into the tablets, along with directly compressible mannitol to enhance mouth feel. Based on invitro dispersion time (approximately 11 seconds), the formulation containing 5% w/w croscarmellose sodium and 40% w/w camphor was found to be show increased invitro drug release (pH 6.8 phosphate buffer). The optimized tablet formulations were compared with conventional commercial tablet formulation drug release profiles. This formulation

showed nearly nine fold faster drug release (t_{50}% 1.8 min) compared to the conventional commercial tablet formulation (t_{50}% 16.4 min). Short term stability studies on the formulation indicated that there are no significant changes in drug content and invitro dispersion time (P 0.05).

Stoltenberg et al., 2011, formulated and evaluated orally disintegrated mini tablets (ODMTs) - A novel solid oral dosage forms for pediatric use. The suitability of five commercially available ready to use tableting excipients , ludiflash, parteck ODTs, pearlitol flash, pharmaburst 500 and prosolv ODTs, to be directly compressed in to mini tablets, with 2mm diameter was examined. All of the excipients are based on co-processed mannitol. Drug free ODMTs and ODMTs with a child appropriate dose of hydrochlorothiazide were investigated. The promising results indicated that the orally disintegrating mini tablets may serve as a novel platform technology for pediatric in future.

Basawaraj S. Patil et al., 2010, formulated and evaluated mouth dissolving tablets of nimesulide by new co processed technique. The two super disintegrants used in this study were croscarmellose sodium and sodium starch glycolate and using the same excipients the tablets were prepared without disintegrants and were evaluated in the similar way. From the results obtained, it can be concluded that the tablet formulation (P_4) showed the promising formulation.

Dinesh Mohan S. et al., 2010, formulated and evaluated salbutamol sulphate fast dissolving tablets were highly accepted fast growing drug delivery system. This study was aimed at fabricating mouth dissolving tablets which can dissolve rapidly in the oral cavity. Asthma is an inflammatory disorder that results in the destruction of air pathways and causes difficulty in breathing however other route of drug delivery

system such as aerosols and parenterals have rapid onset of action but strongly affect the patience compliance. Thus, an attempt was made to improve the onset of action of bronchodilator used commonly in the treatment of asthma. The tablets were prepared by direct compression method using super disintegrants such as primojel, kollidon CL, and L-hydroxy propyl cellulose and evaluated. Formulation FD 9 containing kollidon CL is most acceptable. The fast dissolving tablets of salbutamol sulphate 4% w/w and kollidon CL as the super disintegrant is an alternative to and better than the conventional tablet dosage form used in the management of asthma.

Nagendra kumar D. et al., 2010, formulated and evaluated fast dissolving granisetron HCL tablets using novel co-processed super disintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1, 1:2, and 1:3). The developed super disintegrants were evaluated in comparison with physical mixture of super disintegrants. The angle of repose of the developed excipients was found to be 25^0, carr's index in the range of 10-15% and hausner's ratio in the range of 1.11-1.14. Among the designed formulations (CP_1) containing 4% w/w of co-processed super disintegrant (1:1 mixture of crospovidone and sodium starch glycolate) emerged as the overall best formulation (t_{50}% 2.0 minutes) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t_{50}% 15 minutes). Short term stability studies on promising formulation indicated that there were no significant changes in drug content and invitro dispersion time (P 0.05).

Puttewar T.Y. et al., 2010, formulated and evaluated orodispersible tablets of taste masked doxylamine succinate using ion exchange resins. The difference in drug release values was found to be 100.45±1.89 and 56.47±1.89 respectively. To prevent

the bitter taste and unacceptable odour of the drug, taste was masked with weak cation exchange resins like indion 234, indion 204 and indion 414. Among the three resins, one was selected for further studies i.e. indion 234, because of high drug loading capacity. Drug resin complex were prepared using batch method and effect of various processing parameters viz drug-resin ratio PH, temperature and drug concentration was studied to optimize the loading conditions. Maximum loading was obtained at drug resin ratio 1:2, PH 5, temp $50^0$and drug concentration 4mg/ml. The f_5 batch with disintegration time 25.24 ± 0.75 and dissolution 100.46% ± 3.78 was selected as optimized formulation and this was compared with conventional marketed formulation which was found to be superior.

Sudhir Bhardwaj et al., 2010, formulated and evaluated fast dissolving tablets of aceclofenac using various super disintegrants (sodium starch glycolate) following by direct compression technique. All the formulations showed disintegration time in range of 12.2 to 27.5 seconds along with rapid invitro dissolution. It was concluded that the fast dissolving tablets of poor soluble drug can be made by direct compression technique using selective super disintegrants showing enhanced dissolution, taste masking and hence better patient compliance and effective therapy.

Venkata ramana reddy et al., 2010, compared lyophilization and compression technique of risperidone oral disintegrating tablets (ODTs) using different process like lyophilization and compressed tablets technique. Amberlite was used as taste masking agent, mannitol as a diluent and peppermint as a flavouring agent. The optimized formulation showed good masking less disintegration time (< 30 seconds) and release profile with maximum drug release at all time intervals. It was concluded that risperidone ODT's with improved taste masking and dissolution could be prepared by

both lyophilization and compressed tablet technique with suitable taste masking agent like amberlite.

Vineet Bhardwaj et al., 2010, formulated and evaluated fast dissolving tablets of amlodipine besylate using different super disintegrants and camphor as sublimating agent. Different concentrations (2%, 4%, 6%) of super disintegrants such as Ac-Di - sol, sodium starch glycolate, kollidon-CL were used. Mannitol was used as bulking agent. Tablets were prepared by direct compression. The compressed tablets were dried for 5 hours to allow sublimation of camphor to increase the porosity of the fast dissolving tablets to improve dissolution. All the tablets had hardness of 2.3-3.7kg/cm^2, friability was less than 1% weight variation and drug content were within official limit. Amongst all formulations f_9 prepared by 6%Ac-Di –sol showed least disintegrating time of 11seconds and faster dissolution. Formulation f_9 was then studied for accelerated stability studies as per ICH guidelines for 60 days that shows no remarkable change in the formulation.

Ajay K. Banga et al., 2009, studied effects of disintegration promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. Calcium silicate and various lubricants on an optimized β-cyclodextrin based fast disintegrating tablet formulations were investigated. Effects of moisture treatment were also evaluated at 75, 85 and 95%RH. Results of multiple linear regression analysis revealed that concentration of calcium silicate had no effect; however concentration of lubricant was found to be important for tablet disintegration and hardness. An optimized value of 1.5% of magnesium stearate gave disintegration time of 23.4s and hardness of 1.42kg. Tablet hardness was significantly affected with L-leucine, while other lubricants had no significant effect hardness was not affected at

75% moisture treatment, moisture treatment at 85 and 95% increased hardness of the tablets; however at the same time it negatively affected the disintegration time.

Biraju patel et al., 2009, developed and evaluated fast dissolving tablets of glipizide by direct compression method with a view to enhance patient compliance. Two super disintegrants viz, crospovidone and croscarmellose sodium (4%, 5%, 6%) with different binders viz, PVP K-30 and pregelatinized starch (3%) were used. The prepared batches of tablets were evaluated. Based on evaluating parameters formulation prepared by using 5% croscarmellose sodium with 3% PVP K 30 was selected as optimized formulation. Finally the optimized formulation was compared with marketed conventional formulation. Stability studies carried out at 25^0c/60%RH and 40^0c/75%rh for optimized formulation for 2 months indicated that there was no significant change found in physical appearance, disintegration time and wetting time of the tablets.

Jain C.P. et al., 2009, formulated and evaluated fast dissolving tablets of valsartan using different super disintegrants by direct compression method. Effect of disintegrant on disintegration behavior of tablet in artificial saliva, pH5.8 was evaluated. Wetting time of formulations containing crospovidone was least and tablet showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulation containing crospovidone. The release of valsartan from FDTs was found to follow non fickian diffusion kinetics.

Kawtikar P.S. et al., 2009, formulated, evaluated and optimized fast dissolving tablets containing tizanidine hydrochloride.An attempt has been made to prepare bitter less fast dissolving tablets using eudragit E 100 as a taste masking agent using

mass extrusion technique for preparing taste masked granules. The tablet was prepared with three super disintegrants (e.g.) sodium starch glycolate, cross carmellose sodium and crospovidone. Disintegration in oral cavity tested was found to be 22 seconds. Other tablets were prepared by using camphor as sublimating agent. It was concluded that tablets prepared by addition of superdisintegrants has less disintegration time than those prepared by sublimation method.

Makiko Fuji et al., 2009, studied the effects of powder characteristics on oral tablet disintegration. This report describes an investigation of the factors affecting disintegration time in the mouth (DTM) of rapidly disintegrating tablets. The relation between DTM of rapidly disintegrating tablets and stationary time of upper punch displacement (STP) was examined using a tablet process analyser (Tab all). Results indicated that the bulk density of mixed excipients powder used for tablet preparation affects both DTM and STP. As the value of bulk density increased, STP became longer and DTM shorter. The results of a combination of granules and powder with or without drug showed linear relation between apparent volume (reciprocal of bulk density) and DTM. For a DTM less than 60 seconds, a formulation with a bulk density greater 0.5g/ml should be chosen with a compression force of 5KN. The hardness of tablets could be greater than 3kg if at least one high compressibility excipients was used in the formulation.

Sarasija suresh et al., 2009, formulated designed and optimized fast dissolving clonazepam tablets by direct compression method with a view to enhance patient compliance. Crospovidone (2-8%w/w) was used as super disintegrant and microcrystalline cellulose (20-40%w/w) as diluents, along with directly compressible mannitol to enhance mouth feel. The optimized tablet formulation was compared with

conventional commercial tablet formulation for drug release. This formulation showed nearly fivefold faster drug release (t_{50}%3.5 min) compared to the conventional commercial tablet formulation (t_{50}%16.4 minute).

Shirsand S.B. et al., 2008, designed and evaluated fast dissolving tablets of clonazepam. Three super disintegrants viz, crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with microcrystalline cellulose (Avicel pH 102), along with directly compressible mannitol (pearlitol SD 200) to enhance mouth feel. Among the three promising formulations, the formulation prepared by using 10% w/w of crospovidone and 35% w/w of microcrystalline cellulose emerged as the overall best formulation (t_{50}% 16.4 min). Short term stability studies on the formulations indicated that there were no significant changes in drug content and invitro dispersion time ($P < 0.05$).

Uday S. Rangole et al., 2008, formulated and evaluated rapidly disintegrating tablets of hydrochlorthiazide using different concentrations (2%, 3%, 4%, and 5%) of super disintegrants like croscarmellose sodium and crospovidone by direct compression method using 8mm flat punch. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Crospovidone in the concentration of 4% gave fastest disintegration in 16 seconds and showed 100% drug release within 14 minutes were selected as the optimized formulation. Optimized formulation was subjected to stability studies for thirty days which showed stability with regards to release pattern.

Abdel bary G.et al., 2005, determined the invitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. The disintegration profile of RDT manufactured by main commercialized technologies was evaluated

using the texture analyser (TA) in order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. Results obtained when artificial saliva at 37^0c was employed as disintegration medium were used to correlate the invitro (t_2) and oral disintegration times. Excellent correlation was found as in addition was able to achieve a qualitative measure of the mouth feel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile.

Peter Christian Schmidt et al., 2002, formulated fast dispersible tablets of ibuprofen. A direct compression method was used to prepare these two types of tablets containing coated ibuprofen as a high dosed model drug. The properties of the water dispersible tablet such as porosity, hardness, disintegration time and increase in viscosity after dispersion were investigated. The selected tablet formulation containing 26% galactomennan and 5%, crospovidone disintegrates before the galactomennan starts to swell. These tablets disperse in water within 40 seconds and show a crushing strength of 95N. To develop an orodispersible tablet, a rotatable central composite design was applied to predict the effect of the quantitative factors mannitol and crospovidone as well as compression force on the characteristics of the tablet. Special emphasis was paid to the development of a wetting test, replacing the normal disintegration method an optimum tablet formulation containing 34%mannitol and 13%crospovidone ,provides a short wetting time of 17 seconds and a sufficient crushing strength of 40N.In conclusion fast dispersible tablets with acceptable hardness and desirable taste could be prepared within the optimum region.

Adamofini et al., 1997, developed fast dispersible/ slow releasing ibuprofen tablets to prevent bitter taste and side effects of the drug, the drug was associated with phospholipon 80H, a saturated lecithin by wet granulation. The granules were then coated using different film forming agents (kollicoat SR 30, amprac 01, kollidon 90f, eudragit RD100) obtaining four lots 1-4 coated granules were then formulated with a sweetner (aspartame) a mannitol based diluent (pearlitol SD 200) and kollidon CL (1-4K) or explotab (1-4E) were added as super disintegrants and compacted under low compression force. By an appropriate combination of excipients it was thus possible to obtain orally disintegrating tablets and a delayed release of Ibuprofen using simple and conventional techniques.

Jean Paul remon et al., 1997, formulated and produced rapidly disintegrating tablets by lyophilization using hydrochlorothiazide as a model drug. The influence of different formulation and process parameters on the characteristics of lyophilized oral dosage forms was investigated. Maltodextrins, gelatins, xanthin gum and hydroxy ethyl cellulose were evaluated as excipients in the formulation of freeze dried tablets. The resulting tablets were analyzed for mechanical strength, porosity, disintegration time and residual moisture. The strength of the tablets was enhanced by using higher maltodextrin concentrations. The incorporation of hydrochlorothiazide in the formulations induced a decrease in strength of the tablets. The percentage of HCT released within 10 minutes was 64.55±2.87% and 77.84±8.94% for the reference tablets and the lyophilized tablet formulation respectively. The addition of PEG 6000 (1%w/v) resulted in an increase of drug release as 93.3% from the lyophilized tablets within 10 minutes, however the incorporation of PEG 6000 in the formulation resulted in a decrease in the strength of the tablets.

Yoshiteru watanabe et al., 1997, developed new method of preparing high porosity, rapidly saliva soluble compressed tablets of meclizine using mannitol with camphor as subliming material compressed tablets of water soluble material, prepared using mannitol, did not rapidly dissolve in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, they developed a novel method whereby camphor, a subliming material is removed by sublimation from compressed tablets prepared using a mixture of mannitol and camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15seconds in saliva using mannitol and camphor of meclizine (antidinic agent) tablet with high porosity which dissolves rapidly in saliva.

CHAPTER III

AIM OF THE WORK

CHAPTER – III

AIM OF THE WORK

Hypertension is becoming an important public health challenge worldwide. Hypertension is one of the main risk factors for cardiovascular diseases, which is one of the leading causes of death in developed countries. The relationship between blood pressure and risk of cardiovascular disease is continuous, consistent and independent of other risks.

The higher the blood pressure, the greater is the chance of ischemic heart disease, stroke, heart failure and kidney diseases. Therefore prevention, detection, treatment and control of hypertension should receive high priority.

In the treatment of hypertension, the patient's persistence to therapeutic regimen is very important. The patient should follow the regimen sincerely and should not skip the doses. The most common reasons for noncompliance or non-persistence to antihypertensive therapy are dysphagia (difficulty in swallowing seen in nearly 50% of general population) and during travelling due to non-availability of water to take medication.

Fast onset of action is a major concern in the treatment of hypertension. As the patients with sudden increased blood pressure, there is a marked reduction in functional ability and extreme restlessness. To overcome these problems concept of a patient-friendly tablet i.e. fast-dissolving tablet (FDT) has emerged. Fast dissolving tablets (FDTs) are solid single unit dosage forms that are placed in mouth, allowed to disperse/ dissolve in the saliva without the need of water and provide a quick onset of action. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva

passes down into the stomach. FDTs disintegrate or dissolve in mouth in less than a minute, so there is no need to swallow the tablet or no need of water to take it.

Torsemide is a pyridine sulfonyl urea type loop diuretic indicated for the treatment of hypertension and edema in congestive heart failure. It may be used alone or in combination with thiazide diuretics. It inhibits reabsorption of sodium and chloride in the ascending loop of henle and distal renal tubule, interfering with the chloride-binding co-transport system, thus causing increased excretion of water, sodium, chloride, magnesium and calcium. It does not alter glomerular filtration rate, renal plasma flow, or acid-base balance. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak (Cmax) within 1 hour after oral administration. The drug has a biologic half life of about 3.5hour.

Conventional torsemide tablets available in market are not suitable where quick onset of action is required. To overcome the drawbacks development of FDTs of torsemide improves the patient compliance.

The aim of present work is to prepare fast dissolving tablets of torsemide using super disintegrants (sodium starch glycolate, crospovidone, croscarmellose sodium). The best formulation selection is on the basis of release pattern, disintegration time, wetting time and water absorption ratio.

CHAPTER IV

PLAN OF WORK

CHAPTER – IV

PLAN OF WORK

1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ max

b) Preparation of calibration curve

2. PREFORMULATION (COMPATIBILITY STUDIES)

a) Infrared spectroscopic studies

3. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose

b) Bulk density

c) Tapped density

d) Carr's index

e) Hausner's ratio

f) Drug content for powder blend

4. PREPARATION OF FAST DISSOLVING TABLETS (DIRECT COMPRESSION METHOD)

5. POST COMPRESSIONAL EVALUATION OF FAST DISSOLVING TABLETS

a) General appearance

b) Thickness and Diameter

c) Hardness

d) Weight variation

e) Friability test

f) Drug content

g) Wetting time

h) Water absorption ratio

i) *In-vitro* disintegration test

j) *In-vitro* dissolution test

6. SELECTION AND EVALUATION OF BEST FORMULATION

a) Infrared spectroscopic studies for best formulation

b) Differential scanning colorimetric (DSC) studies for best formulation

c) X-ray diffraction studies for best formulation

d) Stability studies.

CHAPTER V

MATERIALS AND EQUIPMENTS

CHAPTER – V

MATERIALS AND EQUIPMENTS

MATERIALS	DISTRIBUTORS
Torsemide	Micro labs (P) Ltd, Hosur.
Sodium starch glycolate	Pharmafabrikon, Madurai.
Croscarmellose sodium	Pharmafabrikon, Madurai.
Crospovidone	Pharmafabrikon, Madurai.
Mannitol	Nice Chemicals, Cochin.
Microcrystalline cellulose	Central Drug House (P) Ltd, New Delhi, India.
Sodium lauryl sulphate	Rankem Fertilizers &Chemicals Ltd, New Delhi, India.
Sodium saccharin	Central Drug House (P) Ltd, New Delhi, India.
Peppermint flavor	Central Drug House (P) Ltd, New Delhi, India.
Talc	Nice chemicals, Cochin.
Magnesium stearate	Nice chemicals, Cochin.
0.1N HCl	Spectrum Reagents &Chemicals (P) Ltd, Edayar, Cochin.

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A&D Company, Japan.
Single punch tablet compression machine	Cad mach Machinery Co. Pvt, Ahmadabad.
UV Visible spectrophotometer	Shimazdu UV-1700, Japan.
Digital tablet dissolution test apparatus	Lab India Disso apparatus 2000, India.
Friability test apparatus	Indian Equipment corporation, Mumbai.
Tablet hardness tester	Praveen Enterprises, Bangalore.
Vernier caliper	Linker, Mumbai.
Disintegration test apparatus	Rolex, India.
Fourier transform infrared spectroscopy	Shimadzu, Japan.
Differential scanning colorimeter	DSC Q200 V24.4 Instrument, USA.
Powder X-ray diffractometer	XD, Shimadzu, Japan.
Scanning electron microscopy	Hitachi X650, Tokyo, Japan
Environmental Chamber	In lab Equipments (P) Ltd, Madras.

CHAPTER VI

DRUG PROFILE

CHAPTER – VI

DRUG PROFILE

Drug name

Torasemide

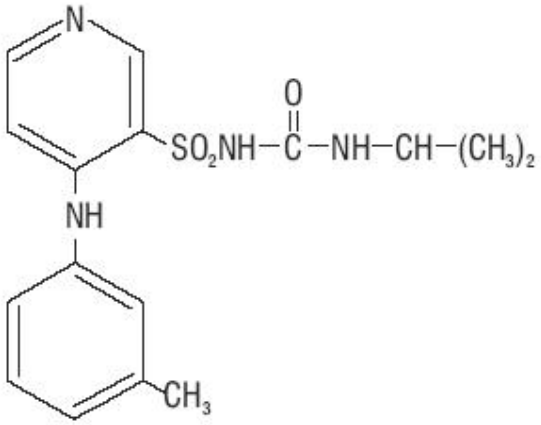
Synonyms

- Torasemidum (Latin)
- Torasemida (Spanish)

Categories

- Anti hypertensive agents
- Diuretics

Structural Formula



Chemical name

1-{4-[(3 methyl phenyl) amino] pyridine -3- sulfonyl}-3- (propan -2-yl) urea.

Molecular formula

$C_{16}H_{20}N_4O_3S$

Description

Nature : White to off white crystalline powder.

Solubility : Slightly soluble in water. The predicted log P value of torsemide is 1.76. But it is soluble in methanol (2mg/ml) and 0.1N HCl.

Melting Point : 164°C

pK_a : 7.1

Molecular weight

348.43 gm/ml

Mechanism of Action:

It inhibits reabsorption of sodium and chloride in the ascending loop of henle and distal renal tubule, interfering with the chloride-binding co-transport system, thus causing increased excretion of water, sodium, chloride, magnesium and calcium. It does not alter glomerular filtration rate, renal plasma flow, or acid-base balance.

Pharmacokinetics

Absorption

Bioavailability is approximately 80%

Volume of distribution

The volume of distribution of torsemide is 12 liters to 15 liters in normal adults or in patients with mild to moderate renal failure or congestive heart failure. In patients with hepatic cirrhosis, the volume of distribution is approximately doubled.

Protein binding

>99%.

Metabolism

Hepatic metabolism accounts for approximately 80% of total clearance. Carboxylic acid derivative, the major metabolite, is inactive.

Route of elimination

Torsemide is cleared from the circulation by both hepatic metabolism (approximately 80% of total clearance) and excretion into the urine (approximately 20% of total clearance in patients with normal renal function).

Half Life

Approximately 3.5 hours.

Indications

- Treatment of hypertension alone or in combination with other antihypertensive agents.
- Treatment of edema associated with congestive heart failure, renal disease, or hepatic disease.

Dosage and administration:

Hypertension

The usual oral initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.

Hepatic Cirrhosis

The usual initial dose is 5 mg or 10 mg of once-daily oral or IV torsemide, administered together with an aldosterone antagonist or a potassium-sparing diuretic.

If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied.

Congestive Heart Failure

The usual initial dose is 10 mg or 20 mg of once - daily oral or intravenous. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Overdosage

- Symptoms include electrolyte depletion, volume depletion, hypotension, dehydration, and circulatory collapse.
- Electrolyte depletion may manifest as weakness, dizziness, mental confusion, anorexia, lethargy, vomiting, and cramps.

Side effects of Torsemide:

The common side effects of torsemide are constipation; dizziness or light headedness when sitting up or standing; excessive urination; headache; increased cough; nasal inflammation; nausea. Seeking medical attention right away should be done if any of these SEVERE side effects occur: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); chest pain; diarrhea; dry mouth or unusual thirst; hearing loss or ringing in the ears; loss of appetite; muscle pain or cramps; rapid or irregular heartbeat; rectal bleeding; restlessness; unusual tiredness or weakness; vomiting.

Drug Interactions

- Coadministration of torsemide was associated with significant reduction in the renal clearance of spironolactone, with corresponding increases in the AUC.

However, clinical experience indicates that dosage adjustment of either agent is not required.

- Because torsemide and salicylates compete for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity when torsemide is concomitantly administered.
- The natriuretic effect of torsemide (like that of many other diuretics) is partially inhibited by the concomitant administration of indomethacin. This effect has been demonstrated for torsemide under conditions of dietary sodium restriction (50 mEq/day) but not in the presence of normal sodium intake (150 mEq/day).
- Coadministration of probenecid reduces secretion of torsemide into the proximal tubule and thereby decreases the diuretic activity of torsemide.
- Other diuretics are known to reduce the renal clearance of lithium, inducing a high risk of lithium toxicity, so coadministration of lithium and diuretics should be undertaken with great caution, if at all. Coadministration of lithium and torsemide has not been studied.
- Other diuretics have been reported to increase the ototoxic potential of aminoglycoside antibiotics and of ethacrynic acid, especially in the presence of impaired renal function. These potential interactions with torsemide have not been studied.

Contraindications

- Allergy to torsemide
- Electrolyte depletion
- Anuria
- Renal failure

- Hepatic coma
- Gout
- Diabetes mellitus
- Lactation

(US Pharmacopoeia, page no-382,

www.drugs.com, www.usfda.com and www.drugbank.com)

CHAPTER VII

EXCIPIENTS PROFILE

CHAPTER – VII

EXCIPIENT PROFILE

CROSPOVIDONE

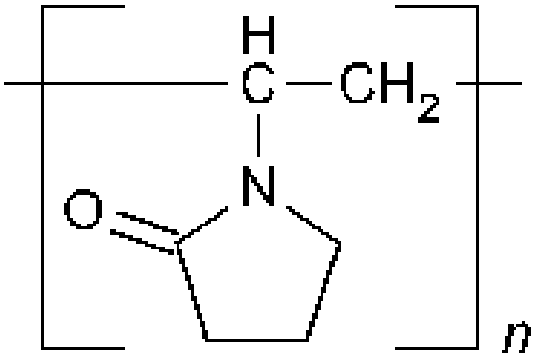
Synonyms:

- Cross linked Povidone.
- Kollidon.
- Polyplasdone.
- Polyvinylpoly pyrrolidone.
- 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer.

Chemical Structure:



Empirical formula:

$(C_6H_9NO)_n$

Molecular Weight:

>1 000 000

Functional category:

Tablet disintegrant.

Application in Pharmaceutical formulation:

- Tablet disintegrant and dissolution agent.
- Solubility enhancer for poorly soluble drug.

Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odourless, hygroscopic powder.

Stability and storage condition:

Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition, 214-216).

CROSCARMELLOSE SODIUM

Synonyms:

- Ac-Di-Sol.
- Cross linked carboxymethylcellulose sodium.
- Explocel.
- Modified cellulose gum.
- Primellose.
- Solutab.
- Vivasol.

Chemical Name:

Cross linked carboxy methyl ether Cellulose sodium salt.

Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation:

Disintegrating agent for tablets and capsules.

Description:

- White or grayish white powder.
- Odourless and tasteless.
- Insoluble in water. Practically insoluble in acetone, ethanol and toluene.

Pharmacopoeial Specifications:

- pH (1% w/v dispersion) 5.0–7.0
- Loss on drying ≤10%
- Heavy metals ≤10 ppm
- Sodium chloride and sodium glycolate ≤ 0.5%
- Sulfated ash 14.0–28.0%

- Settling volume 10.0–30.0 ml
- Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.
- Density (bulk): 0.529 g/cm3
- Density (tapped): 0.819 g/cm3
- Density (true): 1.543 g/cm3

Stability and Storage Conditions:

Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Handling Precautions:

Croscarmellose sodium may be irritant to the eyes; eye protection is recommended. (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition, 211-213).

SODIUM STARCH GLYCOLATE

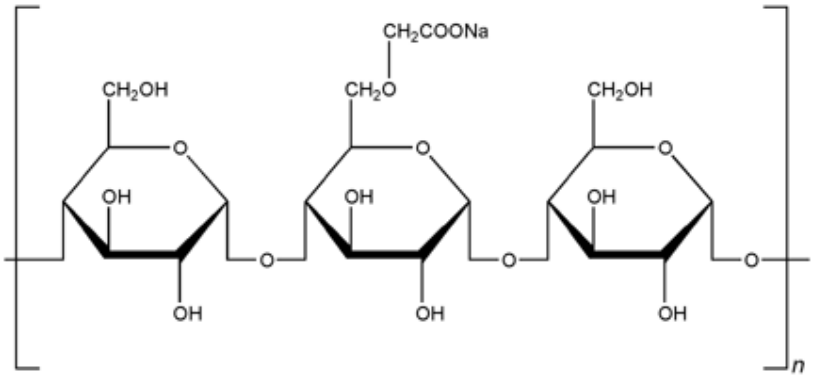
Synonyms:

- Explosol.
- Explotab.
- Primojel.
- Starch carboxymethyl ether, sodium salt.
- Tablo.
- Vivastar P.

Chemical Name:

Sodium carboxymethyl starch.

Chemical structure:



Functional Category:

Tablet and capsule disintegrant.

Application in Pharmaceutical Formulation:

- Sodium starch glycolate is used as a disintegrant in capsule and tablet formulations.
- Sodium starch glycolate is also used as a suspending vehicle.

Description

- Sodium starch glycolate is a white to off-white, odorless, tasteless, free flowing powder
- It does not melt, but chars at approximately 200^{o}C
- It is sparingly soluble in ethanol (95%) but practically insoluble in water.

Pharmacopoeial Specifications:

- Specific surface area: 0.24m2/g;
- Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.
- Viscosity (dynamic): 4200 mPa s (200 cP) for a 4% w/v aqueous dispersion.
- Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

Stability and Storage Conditions:

Sodium starch glycolate should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Handling Precautions:

Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. (Hand book of Pharmaceutical excipients by Raymond C Rowe - 5th edition).

SODIUM LAURYL SULFATE

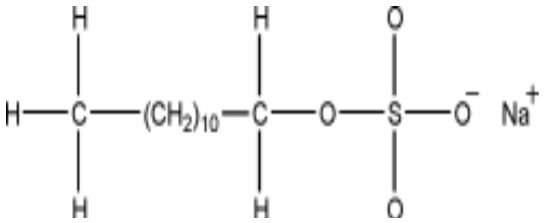
Synonyms:

- Dodecyl sodium sulfate.
- Elfan 240.
- Texapon K12P.
- Sodium dodecyl sulfate.
- Sodium monododecyl sulfate.

Chemical Name:

Sulfuric acid monododecyl ester sodium salt.

Chemical Structure:



Empirical formula:

$C_{12}H_{25}NaO_4S$

Molecular weight:

288.38

HLB value:

≈ 40

Functional category:

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

Application in pharmaceutical formulation and technology:

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non parentral pharmaceutical formulations and cosmetics.

Use	Concentration (%)
Anionic emulsifiers, forms self emulsifying bases with fatty alcohols	0.5–2.5
Detergent in medicated shampoos	≈10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0–2.0
Wetting agent in dentrifices	1.0–2.0

- It is a detergent and wetting agent effective in both alkaline and acidic conditions.
- In recent years it has found application in analytical electrophoretic techniques;SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresisis one of the more widely used techniques for the analysis of proteins.
- The sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).

Description:

SLS consists of white or cream to pale yellow- colored crystals, flakes, or powder having a smooth feel, a soapy. Bitter taste and a faint odour of fatty substances.

Melting point:

204-207°c (for pure substance)

Solubility:

Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Stability and storage condition:

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions i.e. PH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate.

The bulk material should be stored in a well closed container away from strong oxidizing agents in a cool, dry place.

Incompatibilities:

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions. Solutions of sodium lauryl sulfate (PH 9.5-10.0) are mildly corrosive to mild steel, copper, brass, bronze and aluminium.

Sodium lauryl sulfate is also in compatible with some alkaloidal salts and precipitates with lead and potassium.

Handling precautions:

- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Inhalation and contact with the skin and eyes should be avoided; eye protection gloves, and other protective clothing, depending on the circumstances, are recommended.
- Adequate ventilation should be provided or a dust respirator should be worn. Prolonged or repeated exposure should be avoided.
- Sodium lauryl sulfate emits toxic fumes on combustion. (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition, 1811- 1816).

MAGNESIUM STEARATE

Synonyms:

- Magnesium octadecanoat.
- Octadecanoic acid, magnesium salt.
- Stearic acid, magnesium salt.

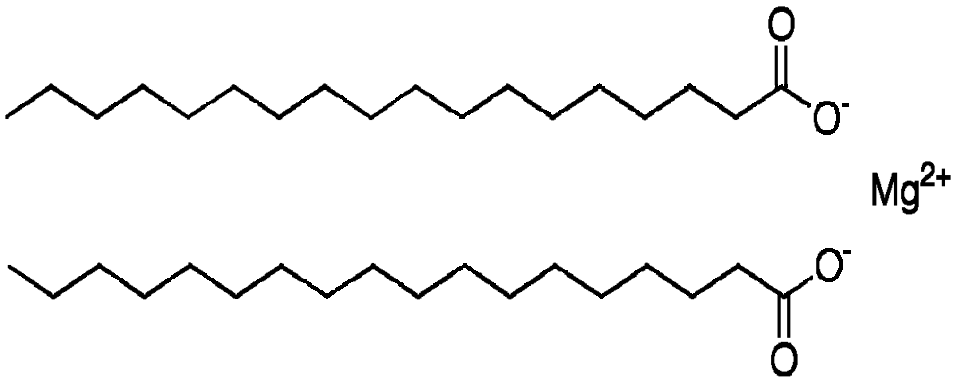
Chemical Name:

Octadecanoic acid magnesium salt.

Structural Formula:

$[CH_3 (CH_2)_{16}COO]_2Mg$

Molecular Structure:



Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ & 591.34

Functional Category:

Tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

- Lubricant in capsule and tablet formulation.(0.25% to 0.25%).
- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is also used in barrier creams.

Description:

- Magnesium stearate is a very fine, light white powder.
- Faint odour.
- Characteristic taste.
- Greasy to the touch and readily adheres to the skin.

Pharmacopoeial Specifications:

Freezing point	5538C
Nickel	45 ppm
Cadmium	43 ppm
Loss on drying	46.0%
Chloride	40.1%
Sulfate	41.0%
Lead	410 ppm

Stability and Storage Conditions:

Magnesium stearate should be stored in a well closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety:

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Handling Precautions:

- ✓ Eye protection and gloves are recommended.
- ✓ Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition, 430-433).

MANNITOL

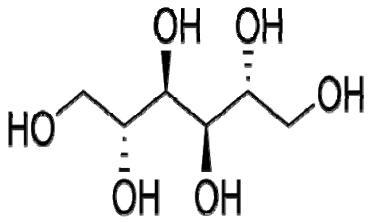
Synonyms:

- Cordycepic acid.
- Manna sugar.
- D-Mannite.
- Pearlitol.

Chemical Name:

D-Mannitol.

Chemical structure:



Empirical Formula and Molecular Weight:

$C_6H_{14}O_6$ & 182.17

Functional Category:

- Diluent.
- Sweetening agent.
- Tonicity agent.

Application in Pharmaceutical Formulation:

- Mannitol is widely used in pharmaceutical formulations and food products.
- It is used as diluents (10–90% w/w) in tablet formulations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations.

- Plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulation.
- It is used as a carrier in dry powder inhalers.
- It is also used as diluents in rapidly dispersing oral dosage forms.
- It is used in food applications as a bulking agent.

Description:

- Mannitol is a white, odorless, crystalline powder, or free-flowing granules.
- It has a sweet taste.
- Microscopically, it appears as orthorhombic needles when crystallized from alcohol.
- Mannitol shows polymorphism.

Pharmacopoeial Specifications:

- Density (bulk):0.430 g/cm3.
- Density (tapped):0.734 g/cm3.
- Density (true): 1.514 g/cm3.
- Dissociation constant: pKa = 13.5 at 188C.
- Flowability: powder is cohesive, granules are free flowing.
- Melting point: 166–168^{o}C.
- Loss on drying: 40.3%.

Stability and Storage Conditions:

It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.

- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.
- Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling Precautions:

Mannitol may be irritant to the eyes; eye protection is recommended. (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition, 449-453).

MICROCRYSTALLINE CELLULOSE

Synonyms:

- Avicel PH.
- Celex.
- Celphere.
- Ceolus KG.
- Ethispheres.
- Fibrocel.
- Pharmacel. .
- Vivapur.

Chemical Name:

Cellulose.

Empirical Formula:

$(C_6H_{10}O_5)$ n

Molecular Weight:

36 000

Functional Category:

- Adsorbent.
- Suspending agent, Tablet and capsule diluents, tablet disintegrant.

Application in Pharmaceutical Formulation:

- Microcrystalline cellulose is used as a binder/diluent in oral tablet and capsule formulations.
- Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation.
- Microcrystalline cellulose is also used in cosmetics and food products.

Description:

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Use Concentration (%)

- Adsorbent: 20–90
- Antiadherent: 5–20
- Capsule binder/diluent: 20–90
- Tablet disintegrant : 5–15
- Tablet binder/diluents: 20–90

Pharmacopoeial Specifications:

- pH: 5.0–7.0
- Loss on drying: 47.0%
- Residue on ignition: 40.05%
- Sulfated ash: 40.1%
- Heavy metals: 410 ppm

Typical Properties:

- Density (tapped):0.478 g/cm3,
- Density (true): 1.512–1.668 g/cm3
- Flowability: 1.41 g/s for Emcocel 90M.
- Melting point: chars at 260–2708C.
- Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Handling Precautions:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. (Hand book of Pharmaceutical excipients by Raymond C Rowe -5th edition132-135).

SACCHARIN SODIUM

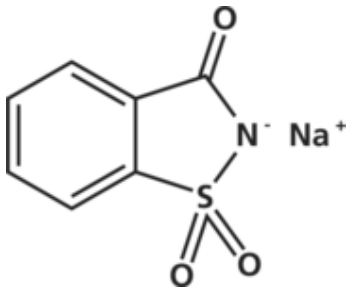
Synonyms:

1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; Crystallose E954; sodium o-benzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

Chemical Name:

1, 2-Benzisothiazol-3(2H)-one 1, 1-dioxide, sodium salt for the dehydrate for the anhydrous material.

Chemical structure:



Empirical Formula:

$C_7H_4NNaO_3S$

Molecular Weight:

205.16

Functional Category:

Sweetening agent.

Application in Pharmaceutical Formulation:

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes; It is also used in vitamin preparations.

Uses of saccharin sodium:

- Dental paste/gel 0.12–0.3%
- IM/IV injections 0.9%
- Oral solution 0.075–0.6%

Description:

Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic after taste that at normal levels of use can be detected by approximately 25% of the population. Saccharin sodium can contain variable amounts of water.

Pharmacopoeial Specification:

- Water 415.0%
- Arsenic 42 ppm
- Selenium 40.003%
- Heavy metals 420 ppm
- Assay (anhydrous basis) 99.0–101.0%

Typical Properties:

- Acidity/alkalinity: pH = 6.6 (10% w/v aqueous solution)
- Density (bulk):0.8–1.1 g/cm3
- Density (particle): 1.70 g/cm3
- Density (tapped): 0.9–1.2 g/cm3
- Moisture content: 14.5% w/w water
- Solvent Solubility at 208C
- Specific surface area: 0.25m2/g

Stability and Storage Conditions:

Saccharin sodium is stable under the normal range of conditions employed in formulations. Saccharin sodium should be stored in a well-closed container in a cool, dry place.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. (Hand book of Pharmaceutican excipients by Raymond C Rowe -5th edition).

TALC

Synonyms:

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore.

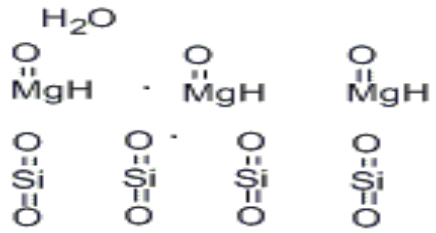
Chemical Name:

Talc

Empirical Formula:

$Mg_6(Si_2O_5)_4(OH)_4$.

Chemical Structure:



Functional Category:

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Applications in Pharmaceutical Formulations:

- Lubricant and diluents.
- Dissolution retardant in the development of controlled-release products.
- An adsorbant.
- Dusting powder.

- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
- Dusting powder: 90.0–99.0%
- Glidant and tablet lubricant: 1.0–10.0%
- Tablet and capsule diluents: 5.0–30.0%

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Pharmacopoeial Specifications:

- Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs): 1.0–1.5
- Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity: 2.7–2.8
- Specific surface area: 2.41–2.42m2/g

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Handling Precautions:

Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. In the UK, the occupational exposure limit for talc is 1 mg/m3 of

respirable dust long-term (8-hour TWA).Eye protection, gloves, and a respirator are recommended. (Handbook of Pharmaceutical excipients by Raymond C Rowe - 5th edition, 641-643).

CHAPTER VIII

EXPERIMENTAL DETAILS

CHAPTER – VIII

EXPERIMENTAL DETAILS

1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ max

Preparation of 0.1N Hydrochloric Acid:

A known volume of 8.5ml Hydrochloric acid is dissolved in distilled water and the volume is made upto 1 litre (USP 21st Revision, NF 16th Edition page no: 1430).

A known weight (100mg) of drug (Torsemide) is dissolved and diluted to 100ml using 0.1N HCl to form a primary stock solution (1000µg/ml). The stock solution is further diluted using 0.1N HCl solution to 10µg/ml concentration. The resultant solution is scanned in the range of (200 – 400nm) by ultra visible spectrophotometer to get absorption maximum (λ_{max}) (Rajesh Shukla *et al*., 2012).

b) Preparation of calibration curve

From the above prepared stock solution, different concentration (1 to 10µg/ml) solutions are prepared using 0.1N HCl solution. The absorbances of these solutions are measured at λ_{max} (288nm) by UV- spectrophotometer. A standard curve is plotted using concentration on X-axis and the absorbance obtained on Y-axis (Nilesh Jain *et al*., 2010).

2. PREFORMULATION (COMPATIBILITY STUDIES)

a) Infrared spectroscopic studies

The FTIR spectrum of pure drug and excipients are recorded on an Infrared spectrometer (Shimadzu, Japan) using KBr discs. The spectrum ranges 4000 to 400 cm^{-1} (Songa Ambedkar Sunil *et al*., 2011).

3. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose (θ)

Angle of repose is determined using fixed funnel method. The blend is poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap(r) is measured and angle of repose is calculated using formula (Manish R. Bhise *et al*., 2013 and Aulton M.E., 2002)

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose,

h = height of pile,

r = radius of the base pile.

The relationship between the angle of repose and powder flow is as follow in the table:

Table 1: Limits for angle of repose

ANGLE OF REPOSE	POWDER FLOW
< 25°	Excellent
25-30 °	Good
30-40°	Passable
>40°	Very poor

b) Bulk density

Apparent bulk density (LBD) is determined by pouring blend into a graduated cylinder .The bulk volume (v_o) and weight of powder (m) is determined. The bulk density is calculated using the formula (Bhingare C.L *et al*., 2013)

$$LBD = \frac{\text{Weight of the powder (m)}}{\text{Volume of the packing } (v_o)}$$

c) Tapped density

The measuring cylinder containing known mass of blend is tapped for a fixed time. The minimum volume (v_t) occupied in the cylinder and weight of powder blend (m) as measured. The tapped density (TBD) is calculated using the formula (Dinesh Mohan S.*et al*., 2010)

$$TBD = \frac{\text{Weight of the powder (m)}}{\text{Tapped volume of the packing } (v_t)}$$

d) Carr's index (I)

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules is determined by carr's compressibility index (c) which is calculated by using the following formula (Devendra Revanand Rane *et al*., 2012)

$$C = \frac{[(TBD - LBD)]}{TBD} X100$$

e) Hausner's ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner ratio} = \frac{\text{Tapped density (TBD)}}{\text{Bulk density (LBD)}}$$

Where TBD is tapped density and LBD is bulk density. Lower hausner ratios (<1.25) indicate better flow properties than higher ones (>1.25) (Devandra Revanand Rane *et al*., 2012).

f) Drug content for powder blend

The Powder blend containing 5 mg equivalent of drug weighed, dissolved and volume is made upto 100ml with 0.1N HCl solution. From the above solution, 5 ml is taken and diluted with 0.1N HCl to obtain (10µg/ml) concentration. The absorbance of resulting solution is measured at 288nm using UV spectrophotometer (shimadzu UV-1700 pharma spec, Japan) and the drug content is estimated (Abdul Hasan Sathali A.*et al*., 2012 and Ganeshan *et al*., 2012).

4. PREPARATION OF FAST DISSOLVING TABLETS (DIRECT COMPRESSION METHOD)

Different tablet formulations are prepared by direct compression technique. Drug, diluents, super disintegrants, surfactant and sweetener are passed through sieve#40. Magnesium stearate is passed through #80 sieve. Required quantity of drug and surfactant is mixed first than other excipients are mixed thoroughly. The resultant powder is compressed using cadmach compression machine equipped with 6mm flat punches by direct compression technique (Jain *et al*., 2011 and Biraju Patel *et al*., 2009).

5. POST COMPRESSIONAL EVALUATION OF FAST DISSOLVING TABLETS

a) General appearance

Five tablets from different batches are randomly selected and organoleptic properties such as colour, odour, taste, shape are evaluated (Ravi Kumar Nayak *et al*., 2011).

b) Thickness and Diameter

Thickness of tablet is determined using vernier caliper (Linker, Mumbai). Three tablets from each batch are used and an average value is calculated (Deepak Sharma *et al*., 2013 and Mahanthesha M.K. *et al*., 2013).

c) Hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study is Monsanto hardness tester,

which applies force to the tablet diametrically with the help of an inbuilt spring and expressed in kg/cm^2 (Kautikwar P.S *et al*., 2009).

d) Weight variation

Weight variation test is done with 20 tablets. It is the individual variation of tablet weight from the average weight of 20 tablets (Deepak Sharma *et al*., 2013 and Indian Pharmacopoeia 2010)

Table 2: Limits for weight variation

Average weight of tablet (mg)	**% Deviation**
80mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

e) Friability test

The friability of tablets is measured using Roche friabilator. Tablets are rotated at 25 rpm for 4 minutes or upto 100 revolutions. The tablets are then reweighed after removal of fines and the percentage of weight loss is calculated (Kautikwar P.S *et al*., 2009 and Anas Bahnassi *et al*., 2012)

$$\% \text{ friability} = \frac{\text{(Initial weight-final weight)}}{\text{Initial weight}} \times 100$$

f) Drug content

The tablet is randomly selected from each batch, weighed individually and powdered. The powder equivalent to 5mg of torsemide are weighed and dissolved in 100 ml of 0.1N HCl solution to obtain the stock solution. From the stock solution suitable dilution are prepared and analysed using UV- spectrophotometer at 288nm (Bhingare C.L *et al*., 2013).

g) Wetting time

The wetting time of the tablets is measured using a very simple process. Five circular tissue paper of 10cm diameter are placed in a petri dish with a 10cm diameter. Ten milliliters of water containing a water soluble dye (eosin) is added to the petri dish. A tablet is carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet is noted as the wetting time (Bhanushali akash k *et al*., 2011).

h) Water absorption ratio

A piece of tissue paper folded twice is placed in a small petridish containing 6ml of water. A tablet is put on the tissue paper and allowed to completely wet. The wetted tablet is then weighed. Water absorption ratio, R is determined using following equation

$$R = \frac{Wa - Wb}{Wa} \times 100$$

Where,

W_a =Weight of tablet after water absorption

W_b= Weight of tablet before water absorption

i) *In-vitro* disintegration test

Disintegration is defined as "state in which no residue of the tablet or capsule remains on the screen of the apparatus". The *in vitro* disintegration time is determined using disintegration test apparatus (Lab India Disso apparatus 2000, India). A tablet is placed in each of six tubes in the apparatus and a disc is added to each tube. Suspend the basket rack in the beaker containing 900 ml of distilled water at 37^0 C and move the basket containing tablets up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no discernible mass remaining in the apparatus are measured (Indian Pharmacopoeia., 1996. Page no: A-80 to A-81 and Hasan Mahmud Reza *et al*., 2012).

Disintegration time

a) Uncoated tablets: 5- 30 minutes
b) Coated tablets: 1-2 hours
c) Fast Dissolving tablets: less than 3 minutes (European Pharmacopoeia)

j) *In-vitro* dissolution test

The release rate of torsemide from fast dissolving tablets is determined using USP dissolution test apparatus II (paddle type). The dissolution test is performed using 900ml of 0.1N HCl at 37 ± 0.5^0c and rotation speed of 50 rpm. A sample of 5ml solution is withdrawn from the dissolution apparatus every 5 minutes for 30 minutes after that 10 minutes time interval for next 30 minutes and the samples are replaced

with fresh dissolution medium. Absorbances of these solutions are measured at 288 nm using UV spectrophotometer. Cumulative percentage drug release is calculated using an equation obtained from a standard curve (Shaikh RG *et al*., 2012 and Puttewar T.Y *et al*., 2010).

6. SELECTION AND EVALUATION OF BEST FORMULATION

a) Infrared spectroscopic studies for best formulation

FDTs of torsemide (Best formulation) are subjected to infrared Spectroscopic studies as per the procedure already discussed in compatibility studies.

b) Differential scanning colorimetric (DSC) studies for best formulation

Differential scanning colorimetry is used for screening. The specified samples is hermetically sealed in a flat bottomed aluminium pans and heated in the differential scanning colorimeter (DSC Q200 V 24.4 Build 116) in an atmosphere of nitrogen and the rate of flow is 25ml/min. temperature range of 0^0 C to 250^0 C is used and the heating rate is 10^0C/min (Preeti Karwa *et al*., 2013).

The pure drug, excipients and final formulation (F27) are subjected to differential scanning colorimetry.

c) X-ray diffraction studies for best formulation

Powder X-ray diffraction pattern is traced employing X-ray diffractometer (XD, Shimadzu, Japan) for the samples, using Ni filtered CuK (α) radiation, a voltage of 45 kV, a current of 20 mA. The samples are analysed over 2θ range of 0-50 ° with scan step size of 0.0170° (2θ) and scan step time 20 s (Setia Anupama *et al*., 2011).

The pure drug, excipients and final formulation (F27) are subjected to X-ray diffraction study.

d) Stability studies.

Stability studies are carried out on optimized formulation. The tablets are RH for duration of two months. After an interval of two months samples are withdrawn and tested for various physical tests and drug release study (Uday S Rangole *et al*., 2008).

CHAPTER IX

RESULTS AND DISCUSSION

CHAPTER - IX

RESULTS AND DISCUSSION

1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ max:

Preparation of 0.1N Hydrochloric Acid:

A known volume of 8.5ml Hydrochloric acid is dissolved in distilled water and the volume is made up to 1 litre (USP 21st Revision, NF 16th Edition page no: 1430).

The absorption maximum (λ max) of the torsemide was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ max) was 288nm in 0.1N HCl which was shown in **Figure 3**(Rajesh Shukla *et al*., 2012 and Nilesh Jain *et al*., 2010).

b) Preparation of calibration curve:

A standard calibration curve for the drug was obtained by measuring absorbance of the solution (1-10µg/ml) at 288nm by plotting the graph of absorbance vs. concentration. The calibration plots of torsemide were shown in **Table 3 and Figure 4**. The linear correlation co efficient was found to be γ= 0.9997. Torsemide obeys beer's law within the concentration range of 1-10 µg/ml (Jain Deepthi *et al*., 2010 and Mishra Bibaswan *et al*., 2010).

2. PREFORMULATION (COMPATIBILITY) STUDIES

a) Infrared Spectroscopic studies (IR):

The Fourier Transform Infra Red Spectroscopy studies were carried out for pure drug, excipients and physical mixtures. The spectra were shown in **Figure 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h &5i.** The spectral analysis of pure drug showed the characteristics peaks at 3425 cm^{-1} , 3351.43 cm^{-1}, 3051.49 cm^{-1}, 1697.41 cm^{-1},1464.98 cm^{-1}, 1357.93 cm^{-1},1081.14 cm^{-1} ,899.82 cm^{-1}. All the above characteristic peaks appear in the spectra of all samples were within the same wavelength number. This indicates that there were no interactions between the drug and physical mixture (Bhingare C.L *et al*., 2013).

3. PRECOMPRESSION EVALUATION FOR POWDER BLEND

a) Angle of repose (θ):

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of all the formulations ranged from 27°11' to 36°69'. The results indicated that all the formulations exhibited good flow properties. The results of angle of repose for all the formulations were shown in **Table 5A & 5B.**

b) Bulk density:

The bulk density was used to determine the free flowing properties of powder blend. The bulk density of all the formulations was in the range of 0.36 - 0.62 g/ml. The values of bulk density showed that the blend was not tightly packed and indicated good flow properties. The results of bulk density for all the formulations were shown in **Table 5A & 5B**.

c) Tapped density:

The tapped density was used to access the free flowing properties of powder blend. Tapped density of all the formulations were in the range of 0.43 - 0.69 g/ml. The results indicated that the blends of all the formulation had good flow properties. The results of tapped density for all the formulations were shown in **Table 5A & 5B.**

d) Carr's index (I):

The Carr's compressibility index was used to access the free flowing properties of powder blend. The compressibility index of all the formulations ranged from 7.13% - 25.01%. This value below 15% indicates a powder having good flow property and good propensity of compression. The results of compressibility for all formulations were shown in **Table 5A & 5B.**

e) Hausner's ratio:

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.07-1.33. It was less than 1.25 indicated better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 5A & 5B.**

f) Drug content for powder blend:

The drug content of the powder blends was used to ensure the therapeutic dosage of the active ingredient in the formulation. The drug content of all the formulations was in the range of 97.04% – 101.49%. The results indicated all the formulations were within the acceptable limits as per USP (USP Limit: not less than 90% and not more than 110%). The results were shown in **Table 5A & 5B.**

4. PREPARATION OF FAST DISSOLVING TABLETS (DIRECT COMPRESSION METHOD)

The fast dissolving tablet of torsemide was prepared by direct compression method using different ratio (2%, 4%, 6%, 8%, 10%, 12%, 14%, 16% and 18%) of superdisintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone). The compositions of the different formulations were given in **Table 4A & 4B.**

Twenty eight formulations (F1-F28) were prepared. All the tablets were white colour and round in shape having 6 mm diameter.

5. POST COMPRESSIONAL EVALUATION OF FAST DISSOLVING TABLETS

The prepared tablets were evaluated on various parameters such as thickness, diameter, hardness, weight variation, friability, drug content, wetting time, water absorption ratio, *in-vitro* disintegration test and *in-vitro* dissolution test. The results were summarized in **Table 6A & 6B.**

a) General appearance:

The formulated tablets were white colour and round shaped. All tablets were elegant in appearance. The results were shown in **Table 6A & 6B.**

b) Thickness and Diameter:

The thickness and diameter of all the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the

thickness of the tablet in all formulation was 3.0mm- 3.2mm and the diameter of the tablet in all formulation was 6mm. The results indicating all the formulations had uniform size and shape. The results were shown in **Table 6A & 6B.**

c) Hardness:

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be 3-4 kg/cm^2. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in **Table 6A & 6B.**

d) Weight Variation Test:

The weight variation test was used to ensure the uniformity of the tablet in all formulations. It was found that the entire tablets passes weight variation test, as the percentage weight variation was within the acceptable pharmacopoeia limits of ±7.5%. The results were shown in **Table 6A & 6B** (Abhishek jain *et al*., 2011).

e) Friability test:

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation was ranged from 0.27 % to 0.83 %. Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in **Table 6A & 6B** (Bhanushali Akash .K *et al*., 2011).

f) Drug content:

The drug content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 97.58 % - 99.19 %. The results indicated all the formulations were within the acceptable limits as per USP (Limit: not less than 90% and not more than 110%). The results were shown in **Table 6A & 6B.**

g) Wetting Time:

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling of water. All the formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in **Table 6A, 6B and Figure 7.**

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F25, F26, F27, F28 showed the wetting time 118, 111, 102, 93, 79, 66, 52, 45, 34, 91, 82, 75, 68, 53, 47, 40, 31, 22, 51, 44, 39, 33, 29, 25, 19, 13, 10, 251 seconds respectively. The results indicated that as the concentration of superdisintegrant increased wetting time was decreased. Formulation F27 containing Crospovidone (18%) shows lesser wetting time than other formulation.

This may be due to fact that Crospovidone and Croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure respectively with minimum gelling. Sodium starch glycolate is disintegrated by swelling mechanism leading to longer wetting time (Raghavendra Rao N.G *et al*., 2010 and Abdul Hasan Sathali A. and Ganesan S. *et al*., 2012).

h) Water Absorption Ratio:

The water absorption ratio test was used to ensure the capacity of the superdisintegrant to absorb the water. The results of water absorption ratio of all the formulation were shown in **Table 6A & 6B.**

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F25, F26, F27, F28 showed the water absorption ratio 50.45%, 51.55%, 58.19%, 68.76%, 75.03%, 77.95%, 79.31%, 80.12%, 83.10%, 27.69%, 41.39%, 50.09%, 50.58%, 55.67%, 58.86%, 61.02%, 60.38%, 62.55%, 62.36%, 66.80%, 76.07%, 77.66%, 79.52%, 82.59%, 85.91%, 89.52%, 91.90%, 23.30%. The results showed that, as concentration of super disintegrant increased water absorption ratio was also increased. Formulation F27 containing Crospovidone shows highest water absorption ratio (91.90%) than other formulation.

The reason for high water absorption ratio for Crospovidone may be due to highly porous structure, it draws large amount of water by water wicking mechanism into porous network of tablet resulting rapidly absorbs water into its network, and highest than formulation prepared with other superdisintegrants. It was indicated that water absorption ratio increased with decrease in wetting time (Arvind S.Singh *et al*., 2010 and Abdul Hasan Sathali. A and Ganesan. S *et al*., 2012).

i) *In-vitro* disintegration test:

The *In-vitro* disintegration time was determined by disintegration test apparatus. Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F25, F26, F27, F28 showed the

disintegration time 146, 145, 136, 124, 114, 107, 98, 94, 87, 127, 119, 115, 110, 94, 87, 77, 82, 76, 94, 83, 74, 65, 71, 67, 64, 57, 53, 274 seconds respectively. It was observed that formulation F27 containing Crospovidone (18%) containing tablet disintegrate rapidly in a short time (53 seconds). The results of disintegration of all the tablets were found to be lesser than 3 minutes (European Pharmacopoeia, 2001) and so satisfied the criteria of fast dissolving tablets. The results were shown in **Table 6A, 6B and Figure 8.**

The faster disintegration time of Crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus these results suggest that the disintegration times can be decreased by using wicking type of disintegrants (Ajay Kumar Patil *et al*., 2011 and Abdul Hasan Sathali. A and Ganesan. S. *et al*., 2012).

j) *In-vitro* dissolution test:

The results of In-vitro drug release studies from fast dissolving tablets of torsemide were shown in the **Table 7A, 7B, 7C, 7D, 7E, 7F & 7G.**

The results showed that the release profiles of different formulations varied according to the type of superdisintegrants and its percentage to the formulations. Maximum percentage of drug (More than 80%) was released from the all formulations within 10 minutes.

Effect of Superdisintegrant on Drug Release:

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 were prepared with 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18% sodium starch glycolate as a

superdisintegrant, showed the cumulative percentage of drug release 93.09%, 93.99%, 92.17%, 90.90%, 90.53%, 88.55%, 96.34%, 91.99%, 95.09% respectively at 10 minutes. Formulation F7 containing 14% sodium starch glycolate shows maximum drug release (96.34%) at 10 minutes. This result indicated that the optimum concentration of sodium starch glycolate was 14%.

The formulation F10, F11, F12, F13, F14, F15, F16, F1, F18 were prepared with 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18% croscarmellose sodium as a superdisintegrant, showed the cumulative percentage of drug release 92.54%, 90.56%, 94.00%, 84.75%, 88.20%, 92.73%, 84.91%, 91.27%, 86.54% respectively at 10 minutes. Formulation F12 containing 6% croscarmellose sodium shows maximum drug release (94.00%) at 10 minutes. This result indicated that the optimum concentration of croscarmellose sodium was 6%.

The formulation F19, F20, F21, F22, F23, F24, F25, F26, F27 were prepared with 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18% crospovidone as a superdisintegrant, showed the cumulative percentage of drug release 92.55%, 89.65%, 92.74%, 90.00%, 89.10%, 90.01%, 95.98%, 93.81%, 99.62% respectively at 10 minutes. Formulation F27 containing 18% Crospovidone shows maximum drug release (99.62%) at 10 minutes. This result indicated that the optimum concentration of crospovidone was 18%.

The formulation F28 were prepared without superdisintegrant, showed the cumulative percentage of drug release of 22.36% at 10 minutes.

From the results, the release rates of superdisintegrants were in the order:

Crospovidone > Sodium starch glycolate > Croscarmellose sodium

The maximum percentage of drug release was achieved by the formulation containing crospovidone (18%) as a superdisintegrant. It may be due to the results in the rapid disintegration of tablet in dissolution medium resulting in maximum drug release.

Among twenty eight formulations, formulation 27 (F 27) was selected as a best formulation because of its lowest wetting time, disintegration time and highest water absorption ratio, drug release (Ravi Kumar Nayak *et al*., 2011).

6) SELECTION AND EVALUATION OF BEST FORMULATION

a) Infrared spectroscopic studies for best formulation:

Infrared spectrum was performed for the fast dissolving tablets, the major peaks of the drug still shown in the spectrum at 3400.62 cm^{-1}, 3348.54cm^{-1}, 2968.55 cm^{-1}, 1654.01 cm^{-1}, 1462.09 cm^{-1}, 1315.5 cm^{-1}, 1083.07cm^{-1}, 881.5 cm^{-1} indicated that there was no interaction between the drug and final formulation in the preparation of fast dissolving tablets. The result was shown in **Figure 5j**.

b) Differential scanning colorimetric (DSC) studies for best formulation:

Any possible drug polymer interaction can be studied by thermal analysis. The DSC thermogram of torsemide was typical of a crystalline substance, exhibiting a sharp endothermic peak at 167.97^{o} C corresponding to its melting and decomposition. The thermograms of the final formulation of torsemide with other excipients showed the existence of the drug endothermic peak which could indicate the absence of interactions between torsemide and other excipients. The DSC thermogram of pure drug and its final formulation is represented in **Figure 6a, 6b, 6c, 6d, 6e, 6f and 6g** (Ravi kumar nayak *et al.*, 2011).

c) X-ray diffraction studies for best formulation:

The PXRD graph of Torsemide, sodium starch glycolate, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium lauryl sulphate and best formulation (F27) were shown in **Figure 11a, 11b, 11c, 11d, 11e, 11f and 11g.** The PXRD spectra of torsemide show numerous distinct peaks for crystallinity at 2θ value of 6.13, 13.45, 17.63, 18.86, 20.88, 22.60, 23.55, 26.04, 28.11 and 28.65 indicating that torsemide present in the highly crystalline form. The major X-ray diffraction peaks of torsemide fast dissolving tablet formulation were suppressed or absent, indicating the decrease in the crystallinity of the torsemide. These results of PXRD were strongly supported by the above DSC observations (Sarita Jangra bhyan *et al*., 2013).

d) Stability studies:

The stability studies were investigated whether the physical chemical parameters and dissolution of fast dissolving tablets is affected by storage under as 40° C ± 2°C and 75%± 5% RH. The best formulation of three batches is stored at 40° C ± 2°C and 75%± 5% RH for two months. The results showed no significant changes in physical appearance, hardness, thickness, drug content, wetting time, water absorption ratio, disintegration time and dissolution test of aged tablets compared to the fresh fast dissolving tablets. This indicates that the fast dissolving tablets were stable under these storage conditions. The results were shown in **Table 8A, 8B and Figure 10.**

TABLES & FIGURES

TABLE 3: CALIBRATION OF TORSEMIDE IN 0.1N HCl

S.No	Concentration(µg/ml)	Absorbance ± SD*
1.	1	0.033 ± 0.001
2.	2	0.067 ± 0.002
3.	3	0.100 ± 0.001
4.	4	0.134 ± 0.002
5.	5	0.166 ± 0.001
6.	6	0.203 ± 0.002
7.	7	0.232 ± 0.003
8.	8	0.264 ± 0.002
9.	9	0.301 ± 0.002
10.	10	0.332 ± 0.002

n=3* **γ= 0.9997**

TABLE 4A: FORMULATION OF FAST DISSOLVING TABLET OF TORSEMIDE

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Torsemide (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sodium starch glycolate (mg)	2	4	6	8	10	12	14	16	18	-	-	-	-	-	-	-	-	-
Croscarmellose sodium (mg)	-	-	-	-	-	-	-	-	-	2	4	6	8	10	12	14	16	18
Crospovidone (mg)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mannitol (mg)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Microcrystalline cellulose (mg)	57.5	55.5	53.5	51.5	49.5	47.5	45.5	43.5	41.5	57.5	55.5	53.5	51.5	49.5	47.5	45.5	43.5	41.5
Sodium saccharin (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Peppermint flavour (mg)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sodium lauryl sulphate (mg)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

TABLE 4B: FORMULATION OF FAST DISSOLVING TABLET OF TORSEMIDE

Ingredients	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**	**F28**
Torsemide (mg)	5	5	5	5	5	5	5	5	5	5
Sodium starch glycolate (mg)	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium (mg)	-	-	-	-	-	-	-	-	-	-
Crospovidone (mg)	2	4	6	8	10	12	14	16	18	-
Mannitol (mg)	30	30	30	30	30	30	30	30	30	30
Microcrystalline cellulose (mg)	57.5	55.5	53.5	51.5	49.5	47.5	45.5	43.5	41.5	59.5
Sodium saccharin (mg)	2	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	1	1	1	1	1	1	1	1	1	1
Talc (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Peppermint flavour (mg)	1	1	1	1	1	1	1	1	1	1
Sodium lauryl sulphate (mg)	1	1	1	1	1	1	1	1	1	1
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100

TABLE 5A: EVALUATION OF MIXED POWDER BLEND OF TORSEMIDE

Formulation code	Angle of repose (°) ± SD*	Bulk density (g/ml) ± SD*	Tapped density (g/ml) ± SD*	Carr's index (%) ± SD*	Hausner's ratio ± SD*	Drug content (%)± SD*
F1	31.58±4.27	0.42±0.00	0.52±0.00	20.01±0.05	1.24±0.00	95.70±1.20
F2	32.39±3.16	0.46±.00	0.58±0.00	21.52±0.03	1.27±0.00	96.10±3.12
F3	29.92±1.62	0.45±0.00	0.57±0.00	20.02±0.03	1.25±0.00	95.00±1.47
F4	30.39±1.46	0.45±0.03	0.49±0.03	07.13±0.09	1.07±0.00	97.48±2.04
F5	33.53±1.62	0.62±0.03	0.69±0.04	09.67±0.48	1.10±0.00	95.98±3.01
F6	29.93±1.50	0.60±0.03	0.66±0.04	09.42±0.44	1.10±0.00	97.38±1.76
F7	30.91±0.32	0.45±0.05	0.51±0.05	12.78±0.48	1.14±0.00	97.68±1.42
F8	30.44±0.81	0.49±0.03	0.57±0.04	13.37±0.89	1.15±0.01	97.38±2.97
F9	30.17±0.28	0.48±0.01	0.55±0.02	13.05±0.48	1.14±0.00	98.69±0.17
F10	28.03±4.10	0.41±0.00	0.48±0.00	13.32±0.01	1.15±0.00	96.58±0.92
F11	27.11±3.37	0.41±0.00	0.48±0.00	13.32±0.00	1.15±0.00	97.68±1.42
F12	33.36±0.27	0.40±0.00	0.50±0.00	18.78±0.03	1.23±0.00	97.38±2.97
F13	30.39±0.35	0.42±0.00	0.52±0.00	19.99±0.06	1.24±0.00	98.69±0.17
F14	36.69±0.29	0.37±0.00	0.45±0.00	17.72±0.00	1.21±0.00	97.48±2.92

n=3*

TABLE 5B: EVALUATION OF MIXED POWDER BLEND OF TORSEMIDE

Formulation code	Angle of repose (°) ± SD*	Bulk density (g/ml) ± SD*	Tapped density (g/ml) ± SD*	Carr's index (%) ± SD*	Hausner's ratio ± SD*	Drug content (%)± SD*
F15	30.73±0.50	0.36±0.00	0.43±0.00	16.70±0.00	1.20±0.00	95.77±4.13
F16	30.42±0.49	0.43±0.01	0.50±0.01	13.05±0.49	1.14±0.00	97.48±2.92
F17	30.23±0.67	0.44±0.03	0.51±0.04	13.37±0.90	1.15±0.01	98.19±0.30
F18	30.59±0.32	0.45±0.03	0.52±0.04	13.33±0.94	1.15±0.01	98.48±1.08
F19	30.60±0.44	0.41±0.00	0.55±0.00	25.01±0.06	1.33±0.00	97.58±1.20
F20	31.30±0.40	0.39±0.00	0.47±0.00	17.69±0.10	1.21±0.00	98.19±0.30
F21	30.33±0.57	0.39±0.01	0.47±0.02	18.00±0.64	1.21±0.01	98.08±1.13
F22	30.33±0.13	0.41±0.02	0.48±0.02	14.86±3.39	1.17±0.04	97.98±1.14
F23	30.33±0.32	0.41±0.01	0.48±0.02	14.58±3.60	1.17±0.05	97.98±1.48
F24	30.56±0.34	0.37±0.00	0.44±0.01	15.68±3.38	1.18±0.04	97.98±0.75
F25	30.95±0.27	0.45±0.03	0.49±0.03	07.13±0.09	1.07±0.00	98.59±1.05
F26	30.33±0.28	0.62±0.03	0.69±0.04	09.67±0.48	1.10±0.00	96.98±0.30
F27	30.98±0.46	0.60±0.03	0.66±0.04	09.42±0.44	1.10±0.00	99.19±0.62
F28	30.64±0.54	0.42±0.01	0.47±0.02	12.77±0.48	1.14±0.00	96.58±0.92

n=3*

TABLE 6A: EVALUATION OF FAST DISSOLVING TABLETS

Formulation code	General appearance	Thickness (mm)	Hardness (kg/cm2)	Average weight (mg)±7.5	Friability (%)	Content uniformity (%)	Disintegration time (sec)	Water absorption ratio (%)	Wetting time (sec)
F1	White colour	3.2	3	99.20	0.83	98.39	146	50.45	118
F2	White colour	3.1	3	95.88	0.34	99.19	145	51.55	111
F3	White colour	3.1	3	98.16	0.58	98.79	136	58.19	102
F4	White colour	3.0	3	97.67	0.51	98.59	124	68.76	93
F5	White colour	3.2	3	98.36	0.41	98.39	114	75.03	79
F6	White colour	3.0	4	98.18	0.53	98.19	107	77.95	66
F7	White colour	3.1	3	98.70	0.41	97.88	98	79.31	52
F8	White colour	3.1	3	98.72	0.36	97.58	94	80.12	45
F9	White colour	3.1	3	98.48	0.35	98.09	87	83.1	34
F10	White colour	3.1	3	98.40	0.4	97.99	127	27.69	91
F11	White colour	3.2	3	98.79	0.43	97.98	119	41.39	82
F12	White colour	3.2	3	98.44	0.56	98.29	115	50.09	75
F13	White colour	3.1	4	98.44	0.32	98.08	110	50.58	68
F14	White colour	3.2	3	98.79	0.27	98.59	94	55.67	53

n=3*

TABLE 6B: EVALUATION OF FAST DISSOLVING TABLETS

Formulation code	General appearance	Thickness (mm)	Hardness (kg/cm2)	Average weight(mg) ±7.5	Friability (%)	Content uniformity (%)	Disintegration time (sec)	Water absorption ratio (%)	Wetting time (sec)
F15	White colour	3.2	4	97.50	0.52	98.19	87	58.86	47
F16	White colour	3.0	3	98.70	0.41	97.88	77	61.02	40
F17	White colour	3.0	3	98.5	0.31	98.59	82	60.38	31
F18	White colour	3.0	3	98.23	0.36	97.88	76	62.55	22
F19	White colour	3.0	3	93.68	0.3	98.59	94	62.36	51
F20	White colour	3.2	3	98.01	0.39	98.49	83	66.8	44
F21	White colour	3.2	4	97.69	0.37	98.09	74	76.07	39
F22	White colour	3.2	3	97.48	0.29	98.49	65	77.66	33
F23	White colour	3.1	3	98.08	0.28	97.88	71	79.52	29
F24	White colour	3.2	3	98.23	0.36	97.88	67	82.59	25
F25	White colour	3.0	3	97.48	0.29	98.49	64	85.91	19
F26	White colour	3.0	3	98.40	0.4	97.99	57	89.52	13
F27	White colour	3.0	3	98.79	0.43	97.98	53	91.9	10
F28	White colour	3.2	3	98.5	0.31	98.59	274	23.3	251

n=3*

TABLE 7A: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F1	F2	F3	F4
5	62.04±0.54	61.32±0.31	59.51±0.31	57.89±0.31
10	93.09±0.31	93.99±0.31	92.17±0.54	90.90±0.31
15	89.91±0.31	93.25±0.54	90.15±0.31	89.78±0.31
20	87.78±0.54	93.04±0.31	88.12±0.30	89.37±0.54
25	88.26±0.54	92.82±0.31	87.16±0.54	89.14±0.31
30	89.28±0.00	92.61±0.54	86.19±0.31	88.54±0.30
40	89.76±0.54	92.20±0.31	82.50±0.31	87.03±0.53
50	89.52±0.62	92.34±0.32	82.58±0.00	84.79±0.54
60	90.18±0.54	91.75±0.32	82.30±0.30	83.25±0.62

n=3*

TABLE 7B: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F5	F6	F7	F8
5	56.80±0.31	57.71±0.54	62.04±0.31	59.33±0.54
10	90.53±0.54	88.55±0.31	96.34±0.31	91.99±0.31
15	88.69±0.31	88.50±0.30	95.79±0.54	91.78±0.31
20	88.09±0.31	88.08±0.31	95.78±0.54	91.38±0.31
25	87.49±0.31	87.84±0.31	96.12±0.54	90.98±0.54
30	86.88±0.31	85.43±0.54	95.92±0.94	89.67±0.31
40	86.63±0.31	84.81±0.54	95.90±0.55	89.07±0.31
50	85.11±0.82	83.82±0.31	95.33±0.55	88.46±0.32
60	82.49±0.53	82.10±0.32	94.22±0.84	87.67±0.30

n=3*

TABLE 7C: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F9	F10	F11	F12
5	64.93±0.54	60.42±0.54	61.50±0.54	63.31±0.31
10	95.09±0.31	92.54±0.31	90.56±0.54	94.00±0.31
15	93.81±0.30	92.15±0.54	90.34±0.31	93.80±0.54
20	92.70±0.31	92.11±0.54	89.93±0.54	93.77±0.54
25	92.67±0.31	91.90±0.63	90.06±0.32	93.56±0.31
30	92.63±0.54	91.67±0.84	90.19±0.63	93.53±0.32
40	92.05±0.54	90.91±0.95	89.60±0.63	92.59±0.54
50	92.00±0.54	89.95±0.85	88.63±0.55	91.83±0.83
60	91.77±0.55	89.17±0.55	87.84±0.32	90.69±0.84

n=3*

TABLE 7D: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F13	F14	F15	F16
5	55.90±0.31	59.51±0.31	62.04±0.54	52.83±0.54
10	84.75±0.31	88.20±0.31	92.73±0.54	84.91±0.31
15	85.76±0.82	88.33±1.74	91.62±0.54	85.20±0.62
20	86.59±0.54	87.91±0.31	90.50±0.94	85.85±1.25
25	87.43±0.63	87.67±0.00	90.09±1.14	86.68±1.66
30	88.26±0.84	88.15±0.00	89.67±0.84	86.97±0.94
40	89.10±0.95	88.44±0.62	88.17±0.56	87.81±0.64
50	89.77±0.95	88.38±0.62	86.66±0.61	87.92±0.02
60	90.43±0.95	88.67±0.83	85.14±0.30	88.57±0.60

n=3*

TABLE 7E: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F17	F18	F19	F20
5	58.61±0.31	52.65±0.31	62.04±0.54	61.14±0.31
10	91.27±0.31	86.54±0.31	92.55±0.31	89.65±0.31
15	91.23±0.31	87.02±0.31	92.52±0.31	89.79±0.31
20	90.29±0.31	88.22±0.54	92.85±0.31	90.28±0.31
25	89.34±0.00	88.88±0.31	92.45±0.62	90.78±0.31
30	88.20±0.54	88.46±0.63	92.59±0.53	90.55±0.31
40	87.95±0.31	89.12±0.01	92.01±0.54	90.50±0.83
50	87.16±0.30	89.78±0.32	92.15±0.30	90.44±0.84
60	84.92±0.31	90.62±0.01	92.46±0.00	90.57±0.31

n=3*

TABLE 7F: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F21	F22	F23	F24
5	64.39±0.31	59.33±0.54	58.79±0.54	59.69±0.82
10	92.74±0.54	90.00±0.54	89.10±0.31	90.01±0.54
15	91.45±0.30	87.97±0.30	89.59±0.31	89.42±0.54
20	90.69±0.82	86.83±0.31	90.45±0.53	89.19±1.57
25	88.84±0.54	84.96±0.53	91.48±0.54	89.14±0.64
30	88.24±0.54	83.25±0.54	91.80±1.12	88.36±1.27
40	87.81±0.31	81.00±0.54	92.66±0.63	88.11±1.45
50	85.21±0.31	78.72±0.54	93.16±0.32	86.96±1.46
60	84.94±0.32	76.97±0.55	93.84±0.82	86.16±1.16

n=3*

TABLE 7G: *IN VITRO* RELEASE PROFILE OF TORSEMIDE FAST DISSOLVING TABLETS

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*			
	F25	F26	F27	F28
5	62.40±0.31	61.14±0.31	66.92±0.54	10.57±0.54
10	95.98±0.54	93.81±0.54	99.62±0.31	22.36±0.82
15	96.33±0.83	93.79±0.54	99.45±0.31	34.77±0.62
20	95.42±1.09	93.40±0.31	99.27±0.00	44.35±0.83
25	93.95±0.32	93.19±0.54	99.28±0.00	53.99±0.55
30	93.38±0.29	92.97±0.31	99.27±0.00	64.04±0.55
40	91.36±0.61	92.39±0.31	98.91±0.31	75.77±0.94
50	90.04±0.82	92.35±0.32	98.36±0.30	90.81±0.55
60	89.26±0.53	91.22±0.32	97.80±0.31	95.82±0.62

n=3*

TABLE 8A: STABILITY STUDY OF BEST FORMULATION (F27) AT 40° C ± 2°C AND 75%± 5%

PARAMETERS	INTERVAL OF TESTING		
	AT 0 MONTH	AT 1MONTH	AT 2MONTH
Physical appearance	White colour	White colour	White colour
Hardness ($kg/cm^{2)}$	3	3	3
Thickness (mm)	3	3	3
Wetting time (sec)±SD*	10	14	15
Water absorption ratio(%)±SD*	91.90±0.57	91.39±0.59	91.20±0.43
Disintegration time (sec)±SD*	53	56	57
Drug content (%)±SD*	97.98±0.15	97.38±0.76	97.15±0.42

TABLE 8B: DISSOLUTION PROFILE OF BEST FORMULATION (F27) AT 40° C ± 2°C AND 75%± 5%

Time interval (min)	Percentage of drug release (%) ± SD*		
	AT 0 MONTH	AT 1MONTH	AT 2MONTH
5	66.92±0.54	65.65±0.31	65.29±0.54
10	99.62±0.31	98.53±0.31	98.17±0.54
15	99.45±0.31	98.35±0.31	98.17±0.54
20	99.27±0.00	98.17±0.54	97.99±0.32
25	99.28±0.00	98.17±0.54	97.80±0.32
30	99.27±0.00	98.16±0.54	97.79±0.32
40	98.91±0.31	97.61±1.08	97.42±0.83
50	98.36±0.30	97.59±1.09	97.22±0.63
60	97.80±0.31	97.03±0.55	96.83±0.32

n=3*

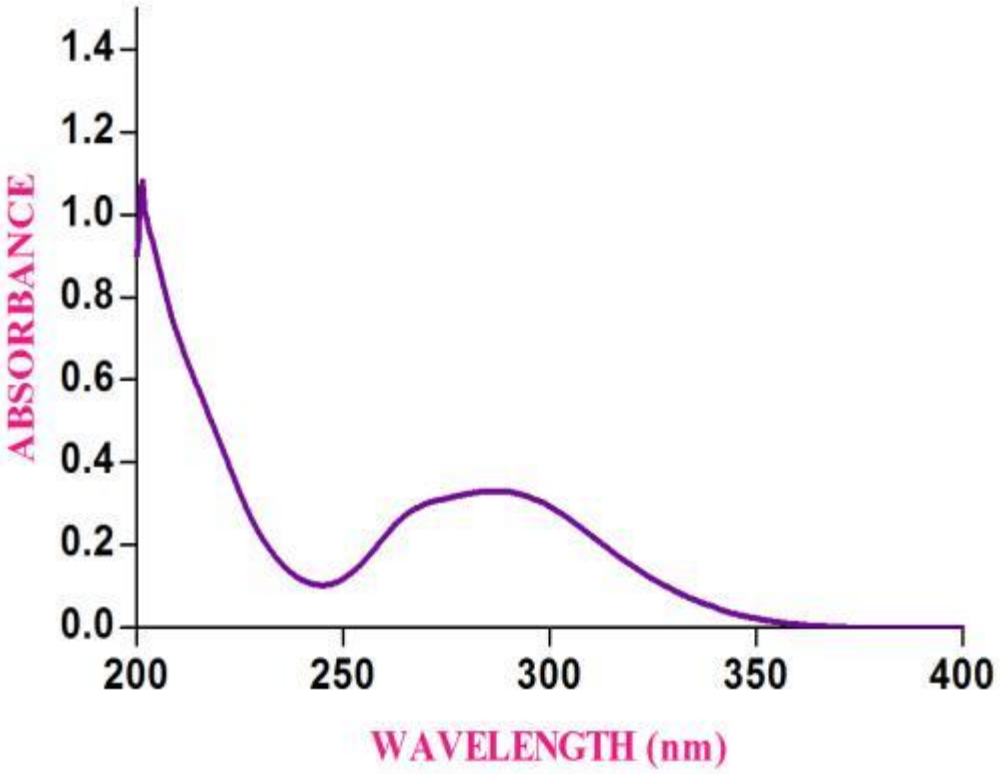


Figure 3: Determination of λmax of Torsemide

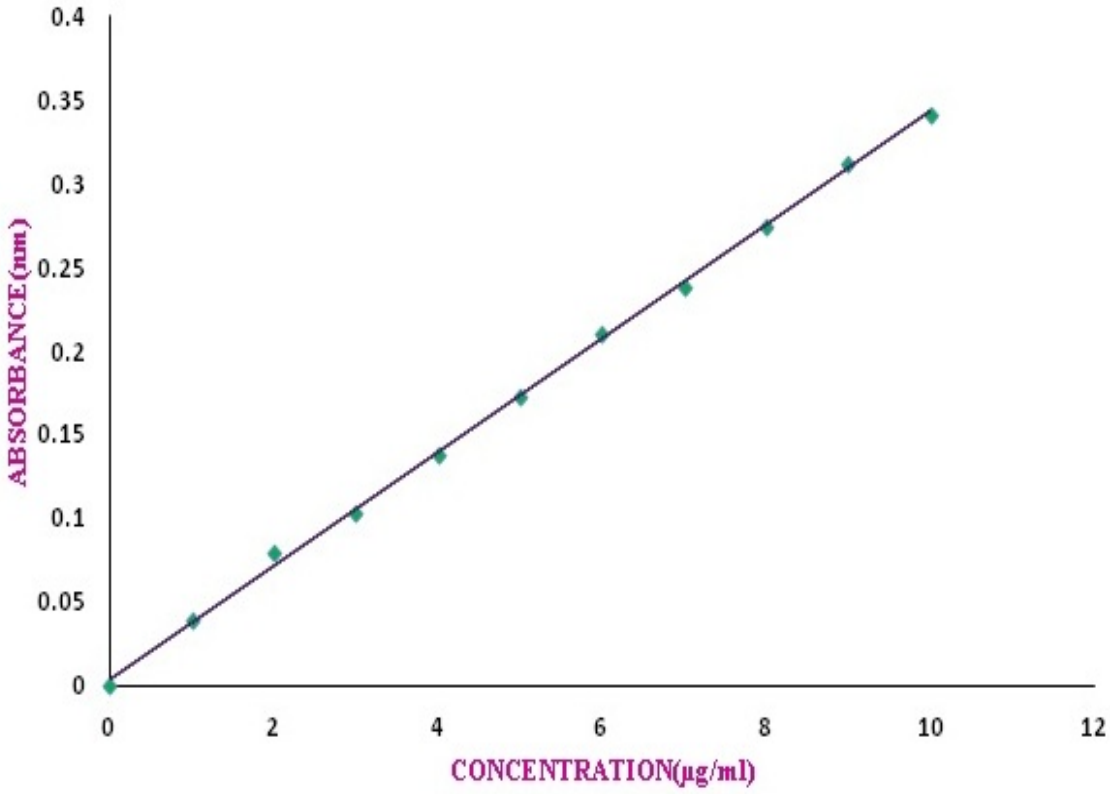


Figure 4: Calibration curve of Torsemide in 0.1N HCl

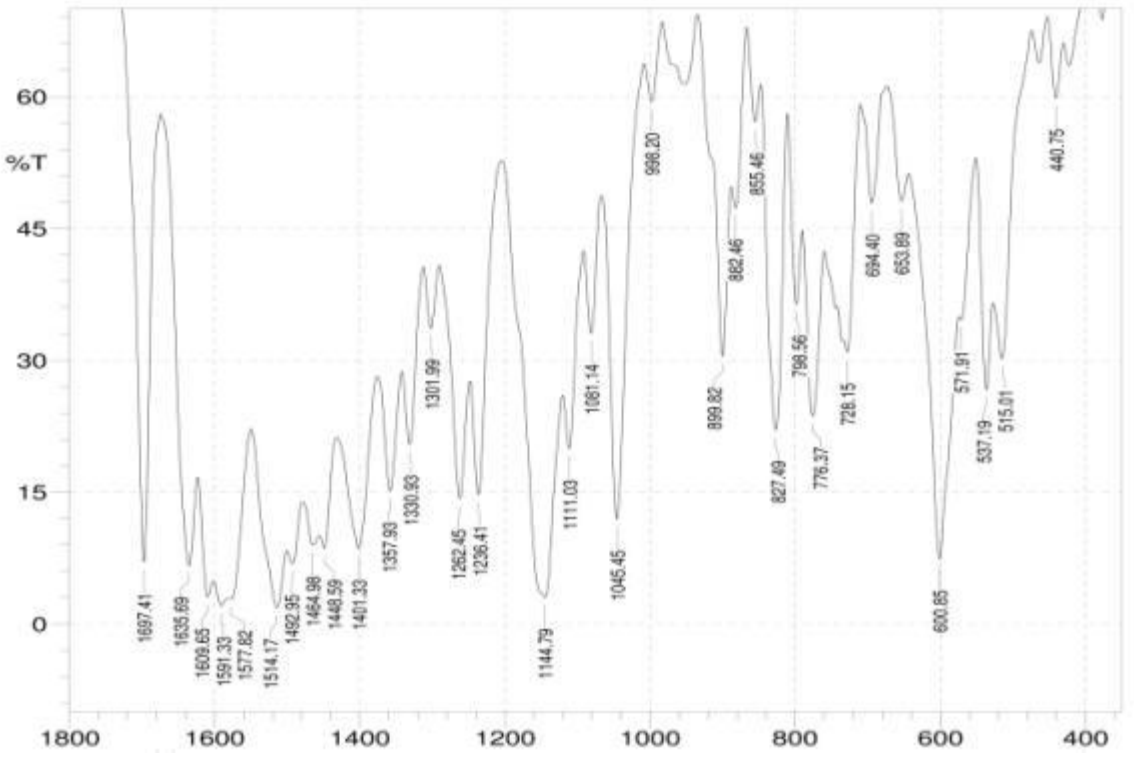


Figure 5a: FT-IR spectrum of Torsemide

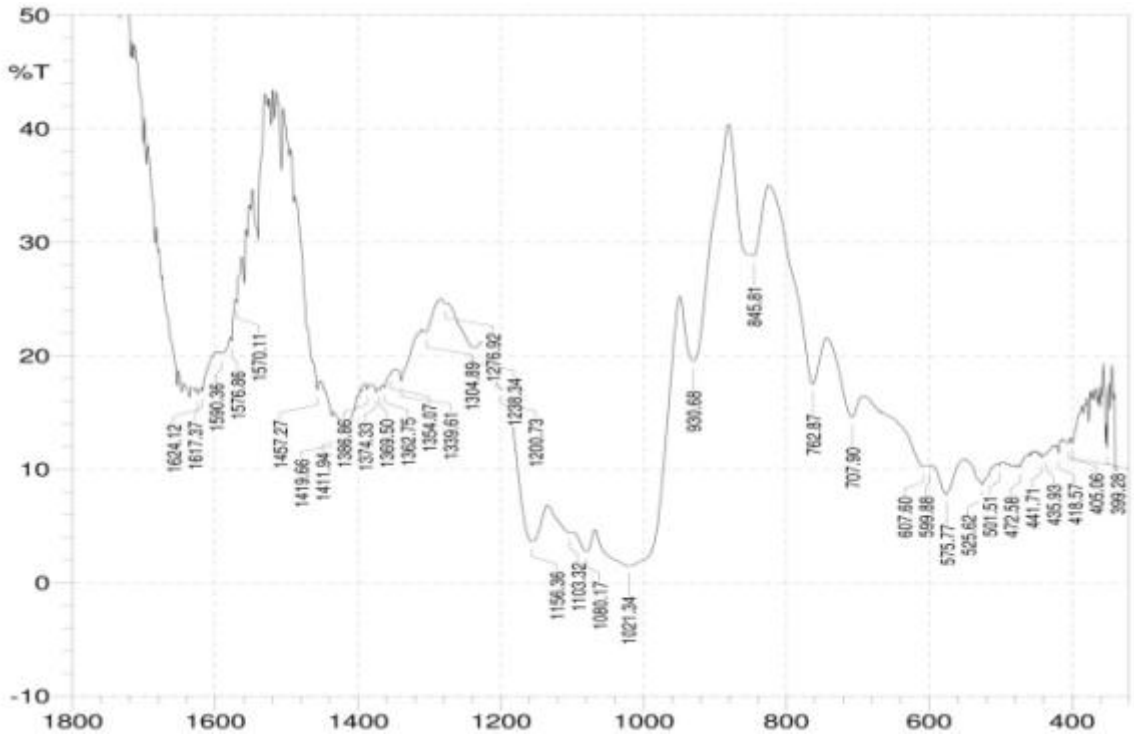


Figure 5b: FT-IR spectrum of sodium starch glycolate

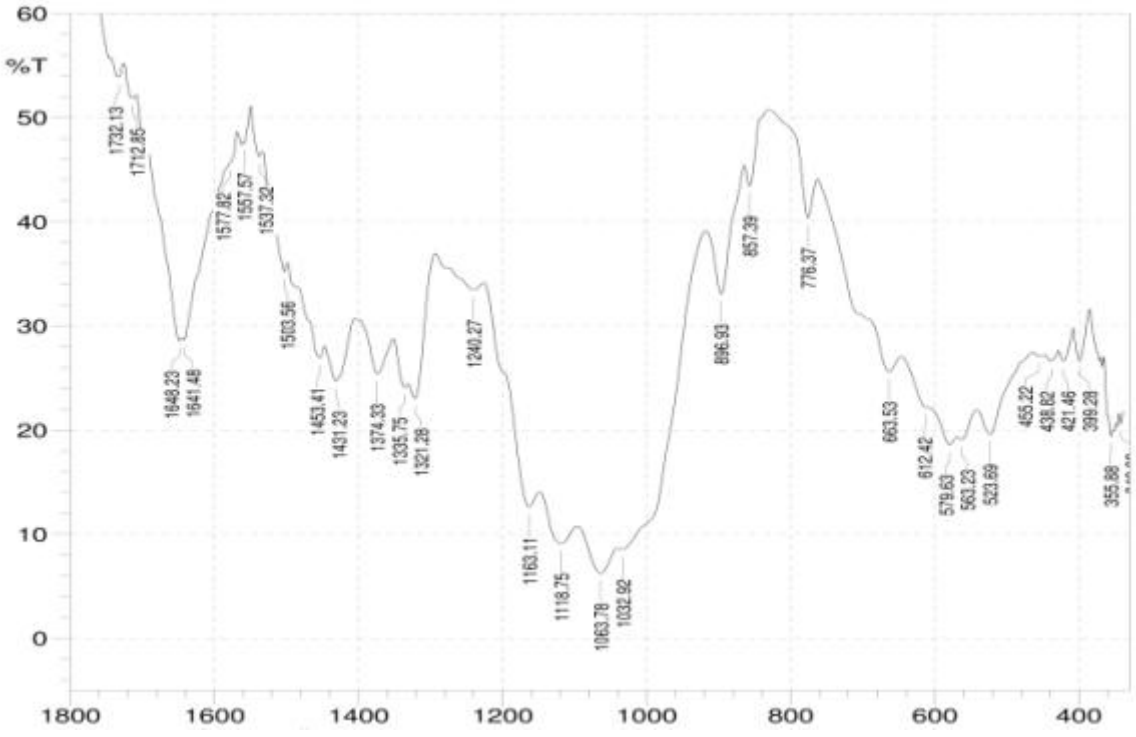


Figure 5c: FT-IR spectrum of croscarmelose sodium

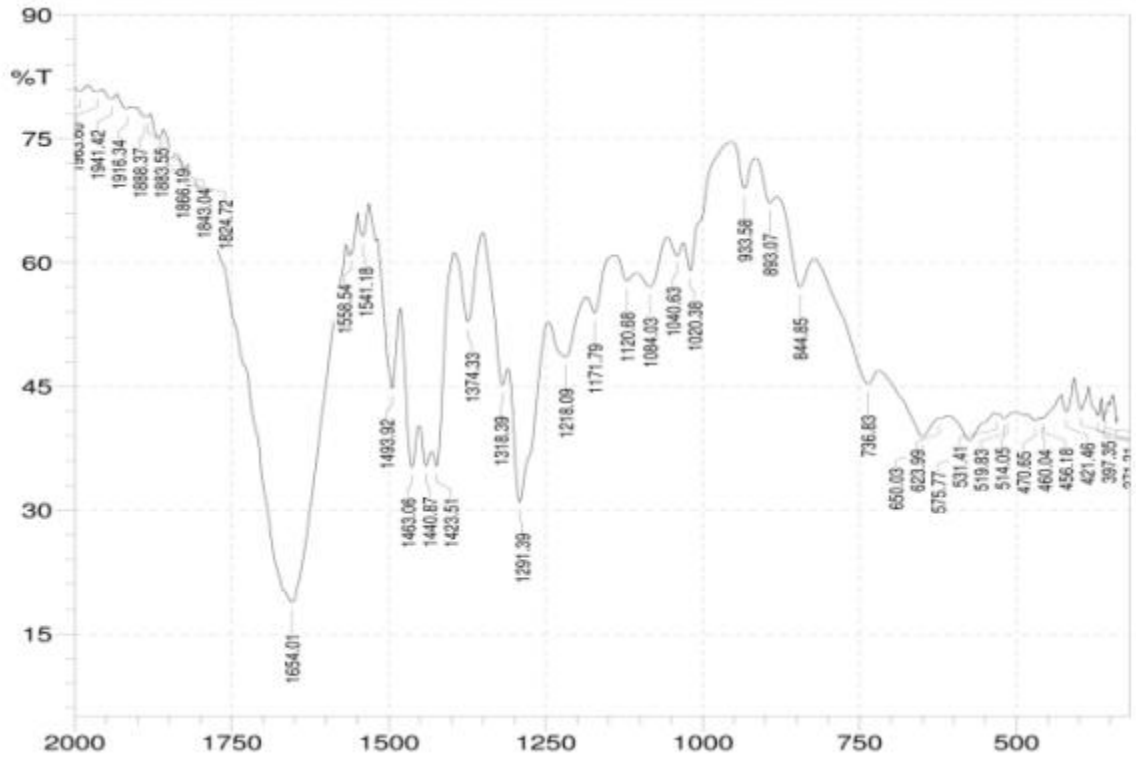


Figure 5d: FT-IR spectrum of crospovidone

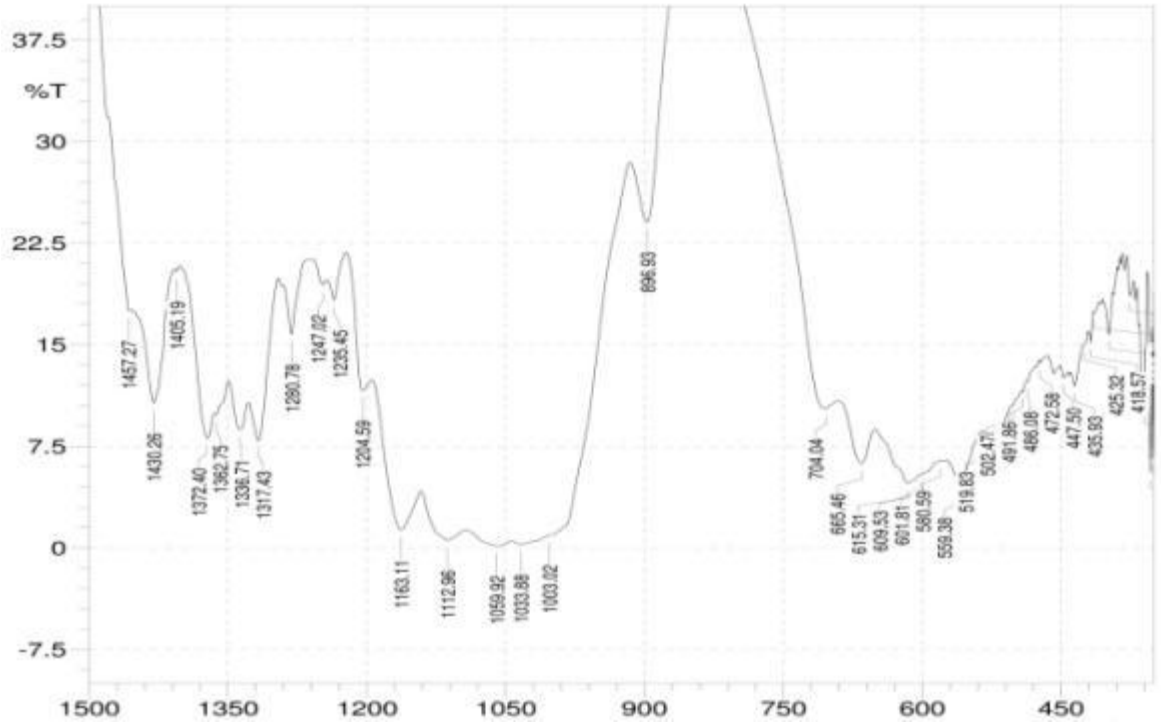


Figure 5e: FT-IR spectrum of microcrystalline cellulose

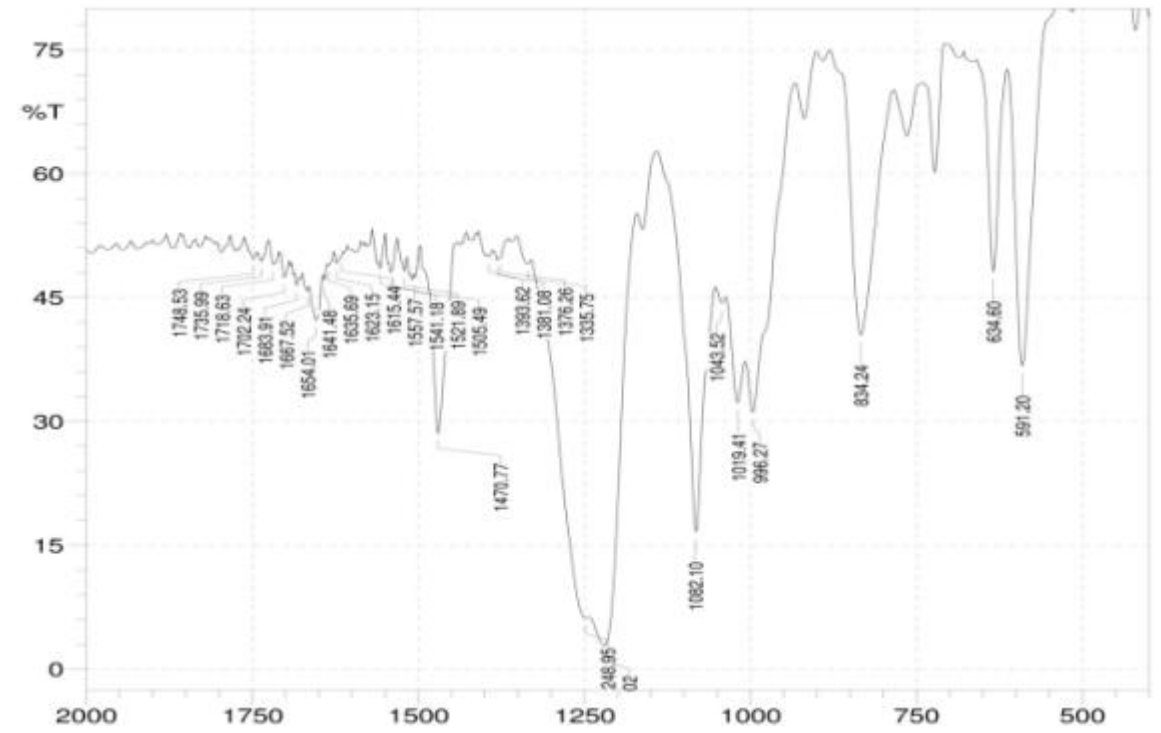


Figure 5f: FT-IR spectrum of sodium lauryl sulphate

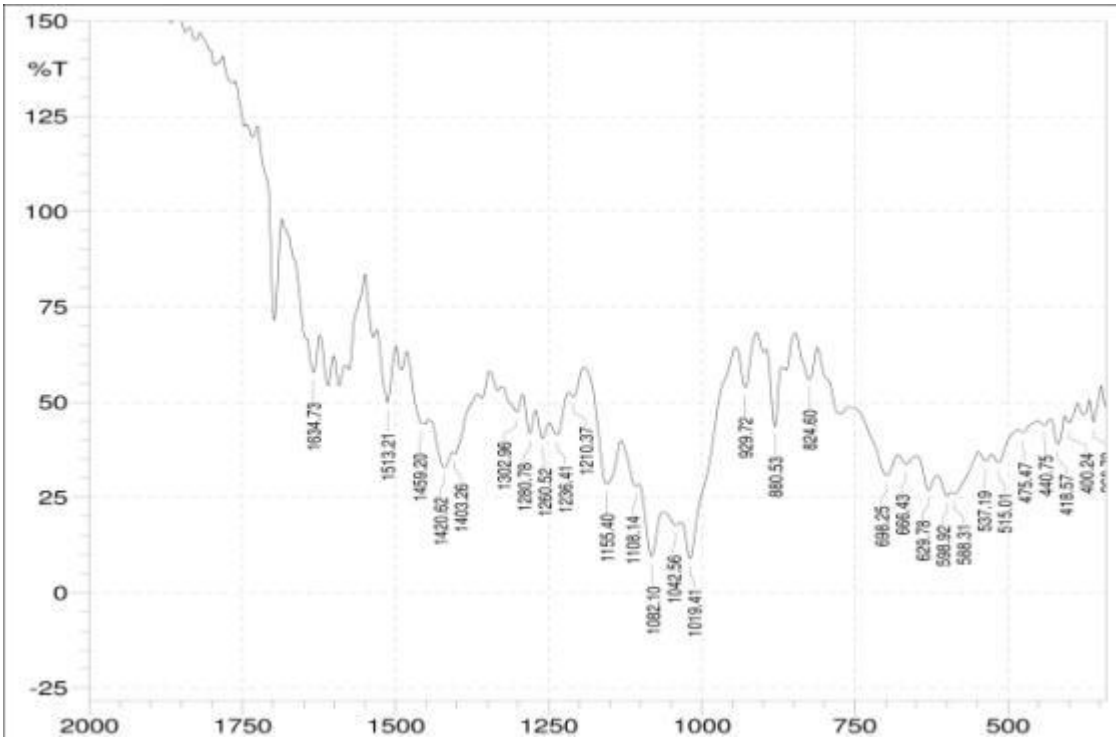


Figure 5g: FT-IR spectrum of Torsemide + sodium starch glycolate + microcrystalline cellulose + sodium lauryl sulphate

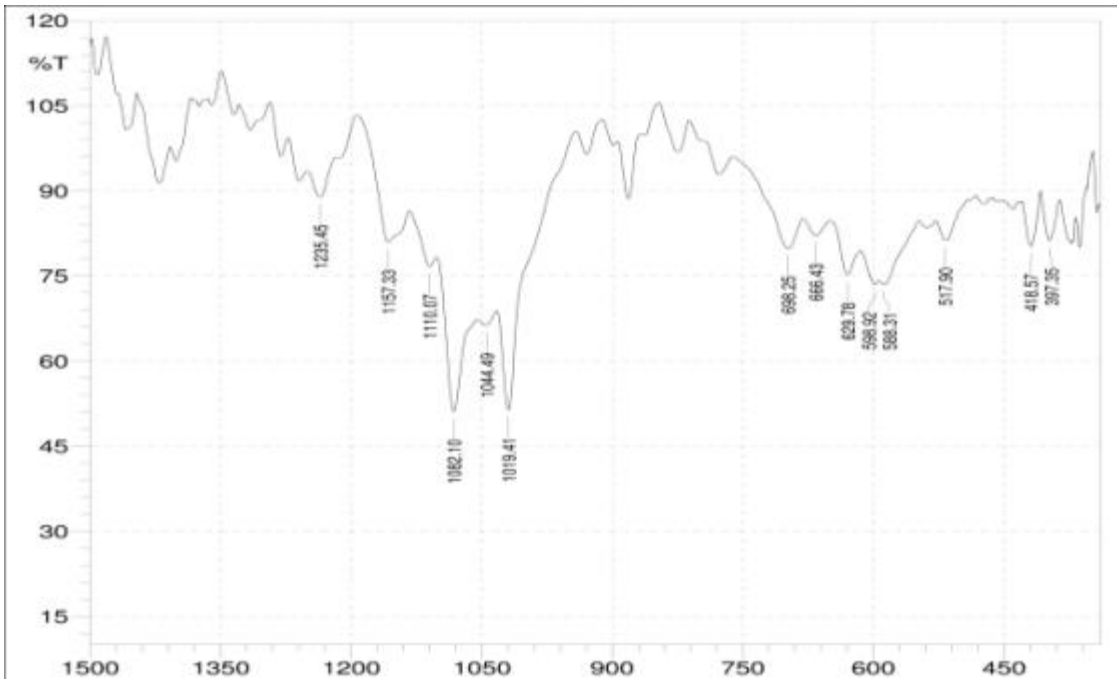


Figure 5h: FT-IR spectrum of Torsemide + croscarmelose sodium + microcrystalline cellulose + sodium lauryl sulphate

Figure 5i: FT-IR spectrum of Torsemide + crospovidone + microcrystalline cellulose + sodium lauryl sulphate

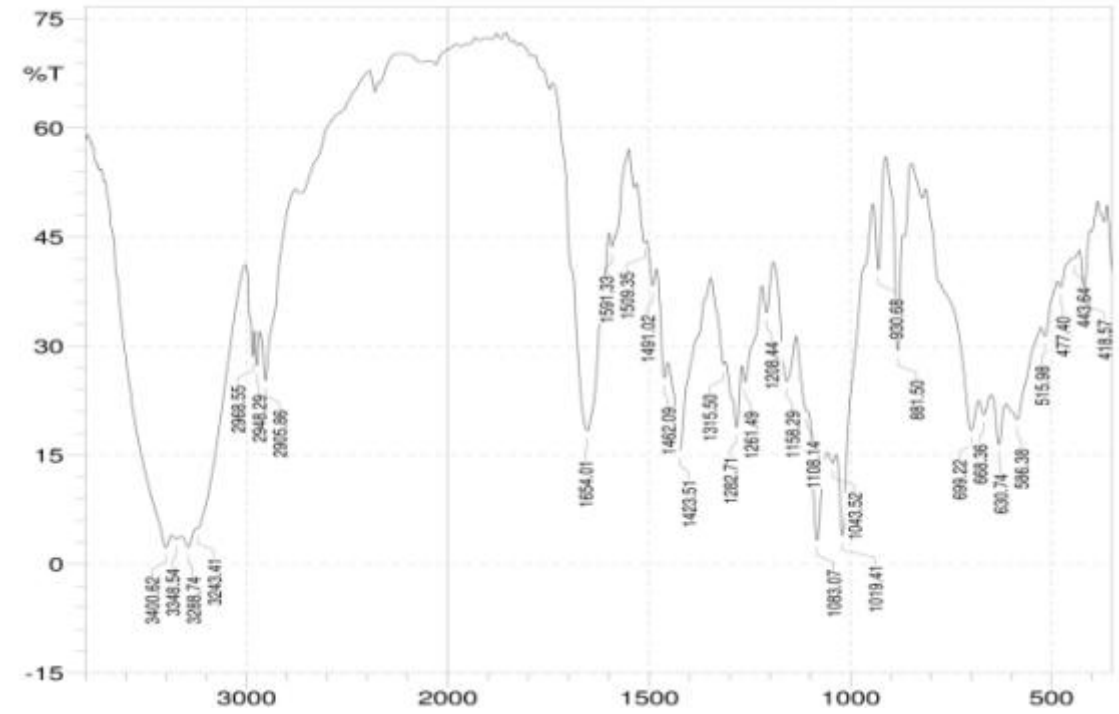


Figure 5j: FT-IR spectrum of Torsemide fast dissolving tablet

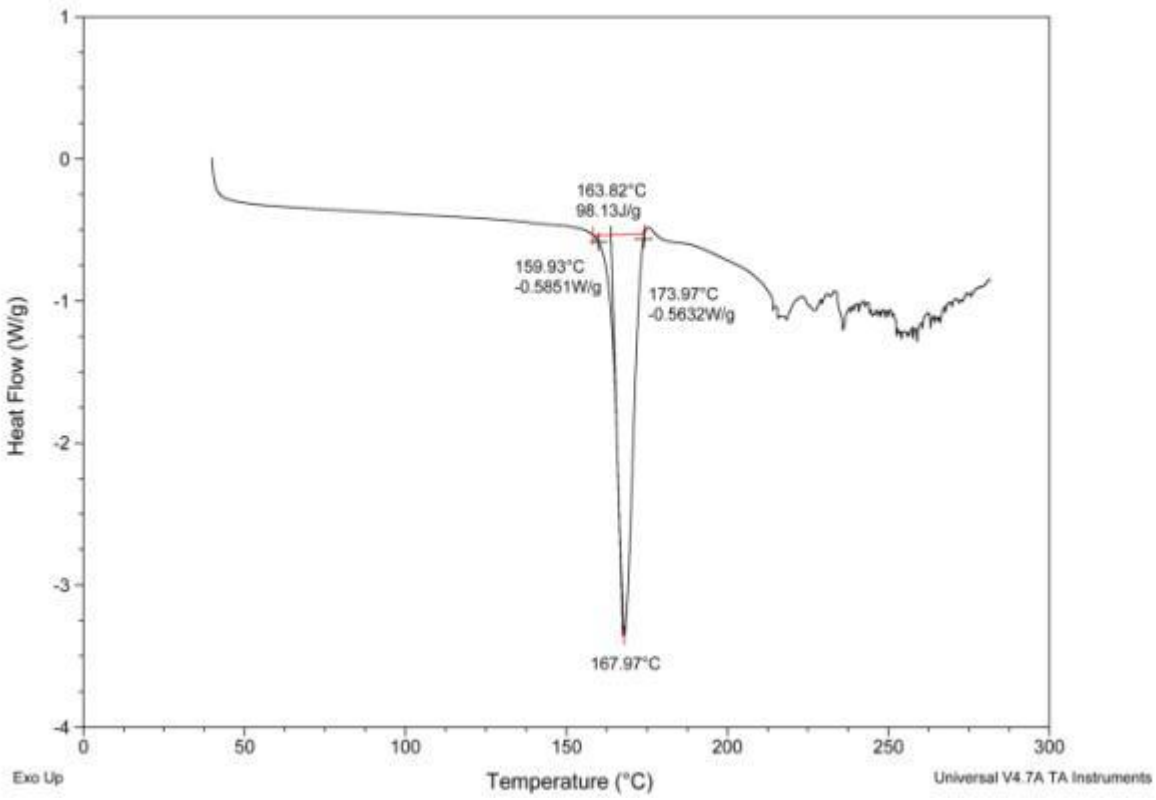


Figure 6a: DSC thermogram of Torsemide

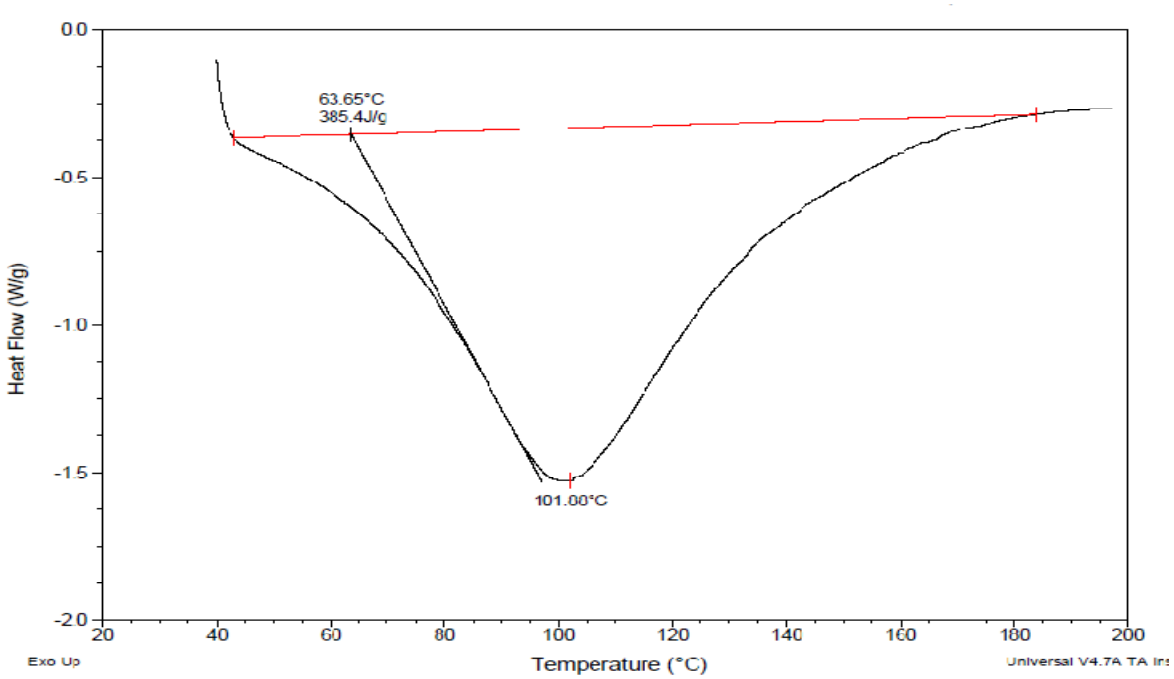


Figure 6b: DSC thermogram of sodium starch glycolate

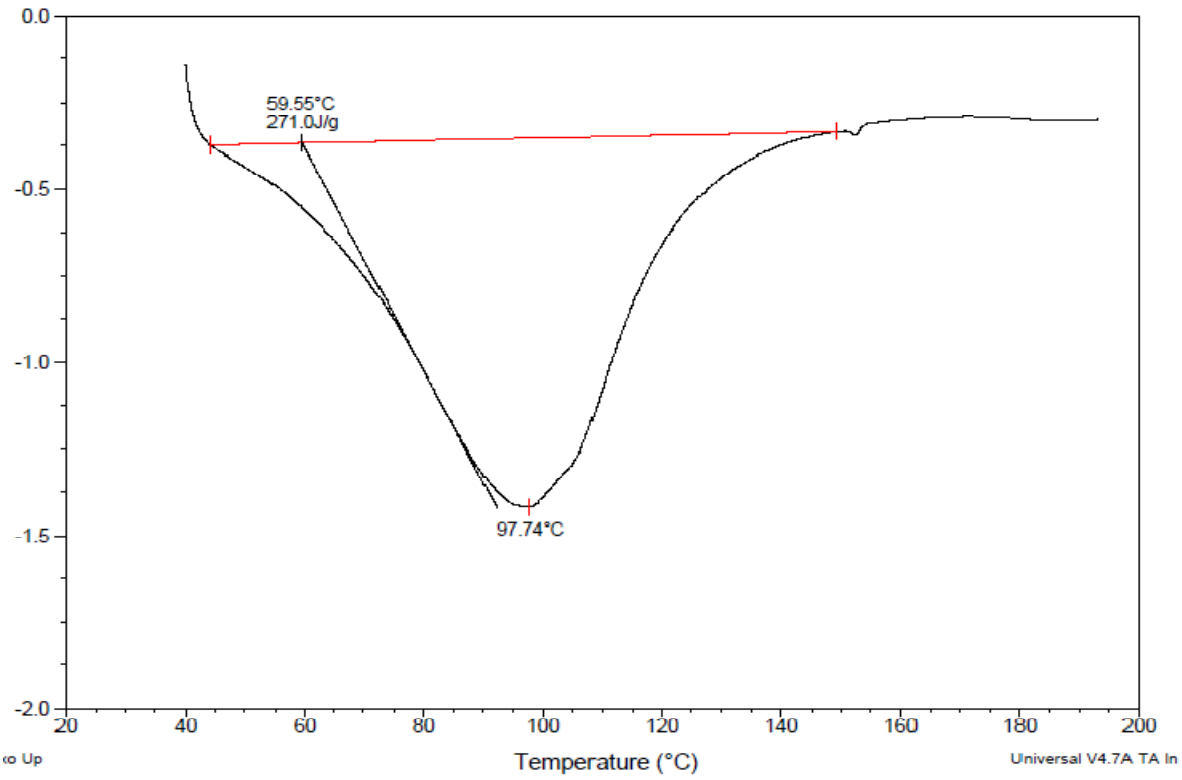


Figure 6c: DSC thermogram of croscarmelose sodium

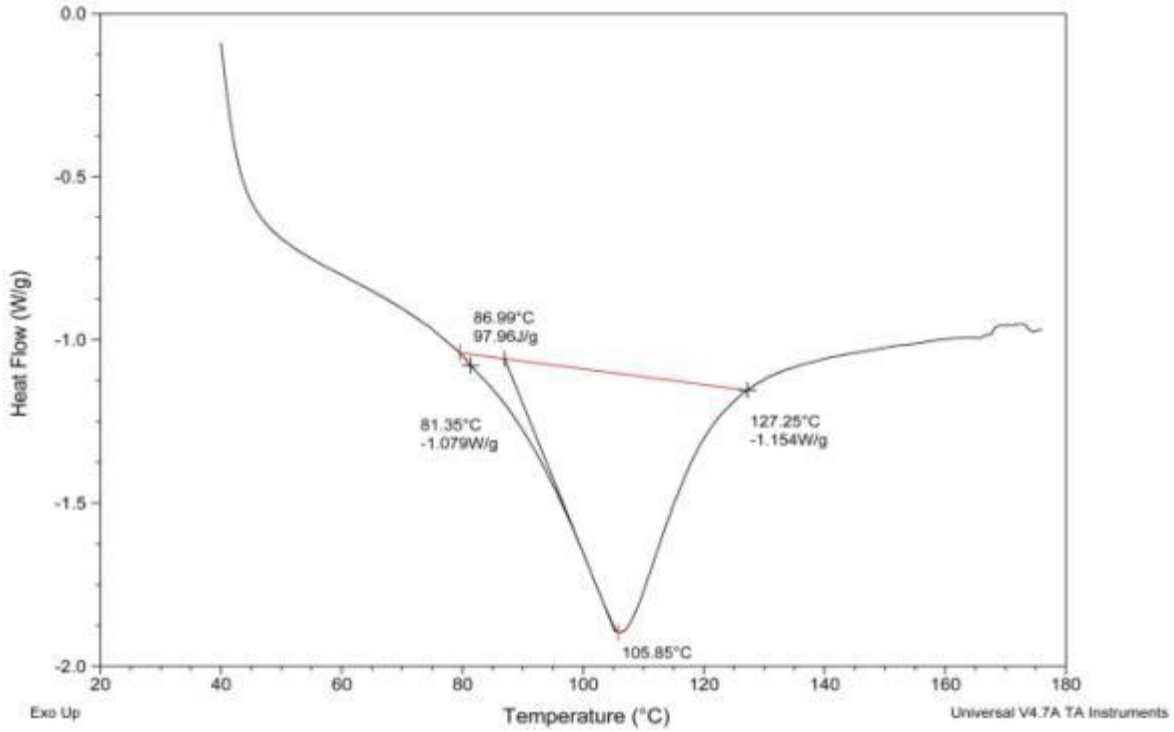


Figure 6d: DSC thermogram of crospovidone

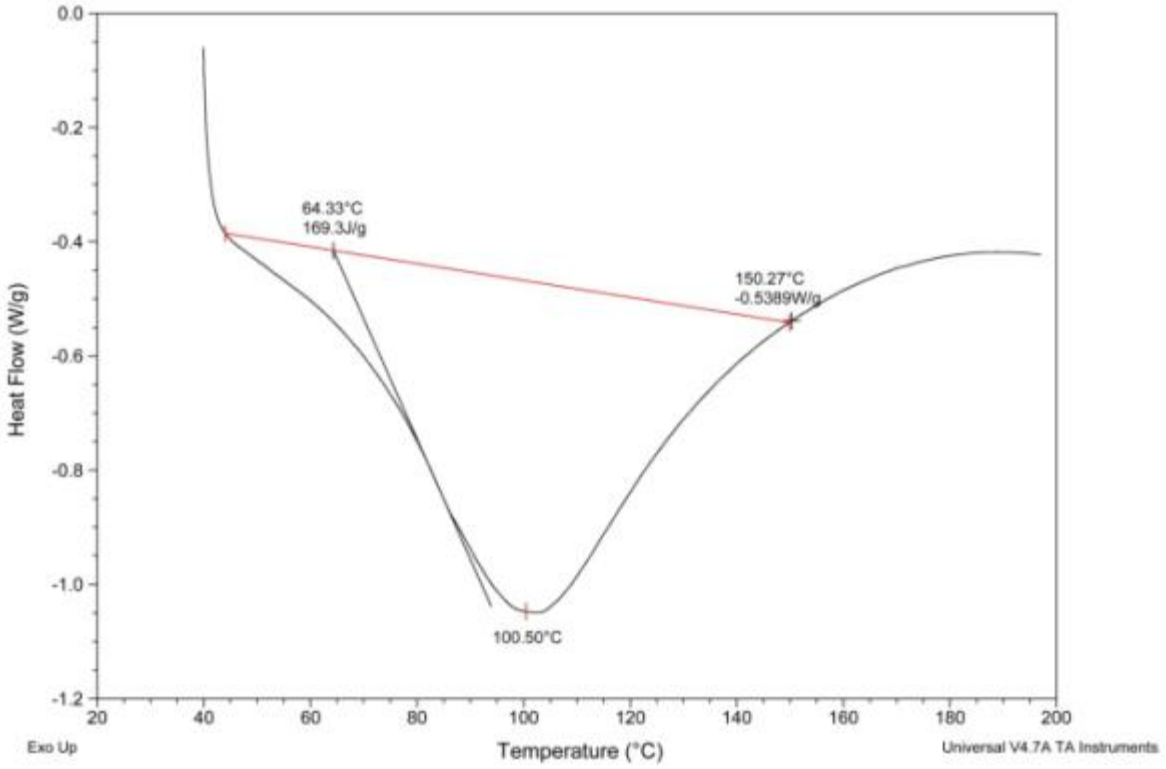


Figure 6e: DSC thermogram of microcrystalline cellulose

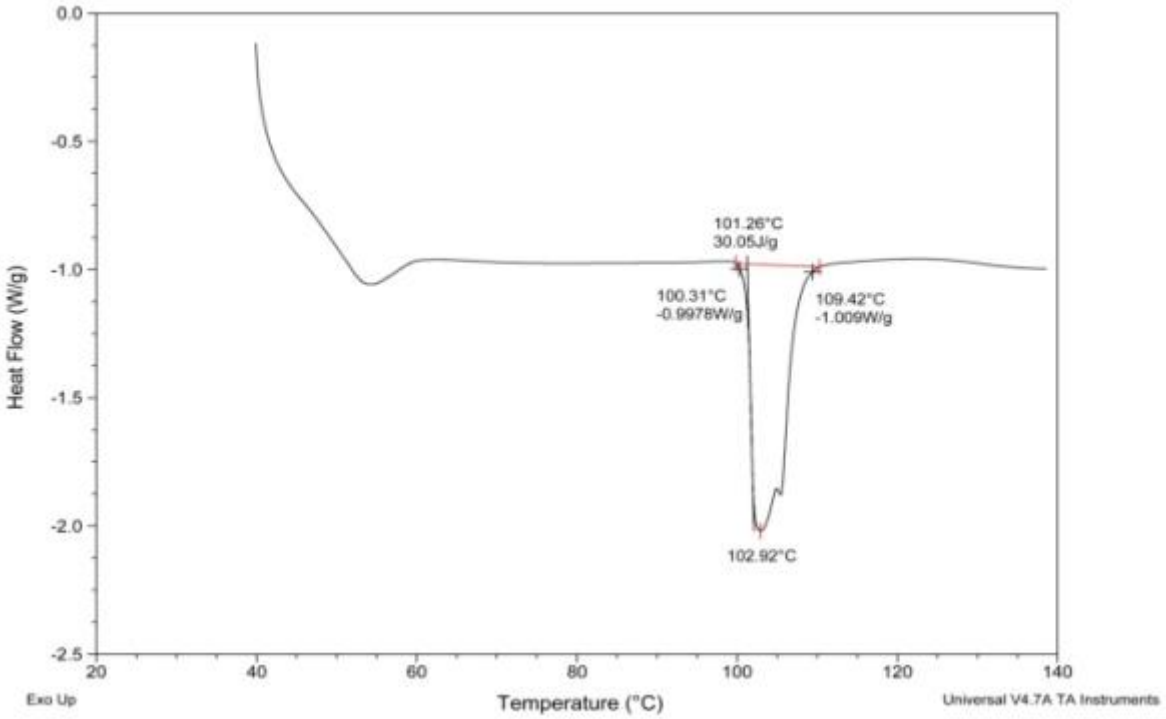


Figure 6f: DSC thermogram of sodium lauryl sulphate

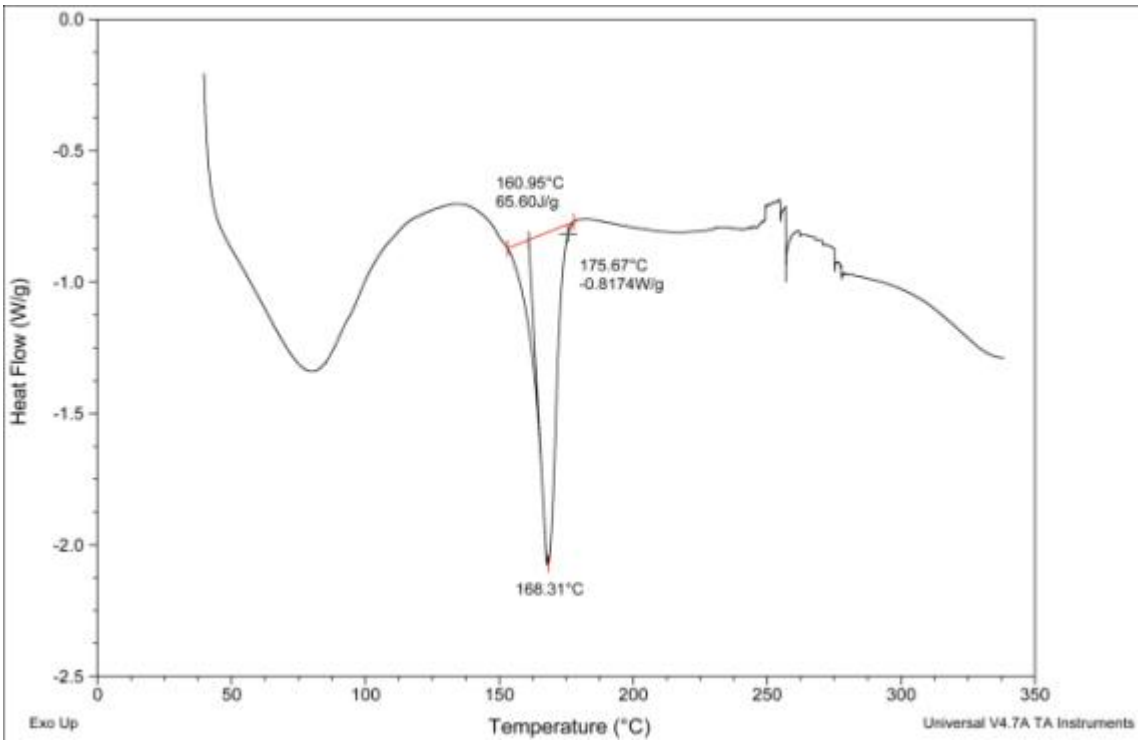


Figure 6g: DSC thermogram of Best formulation

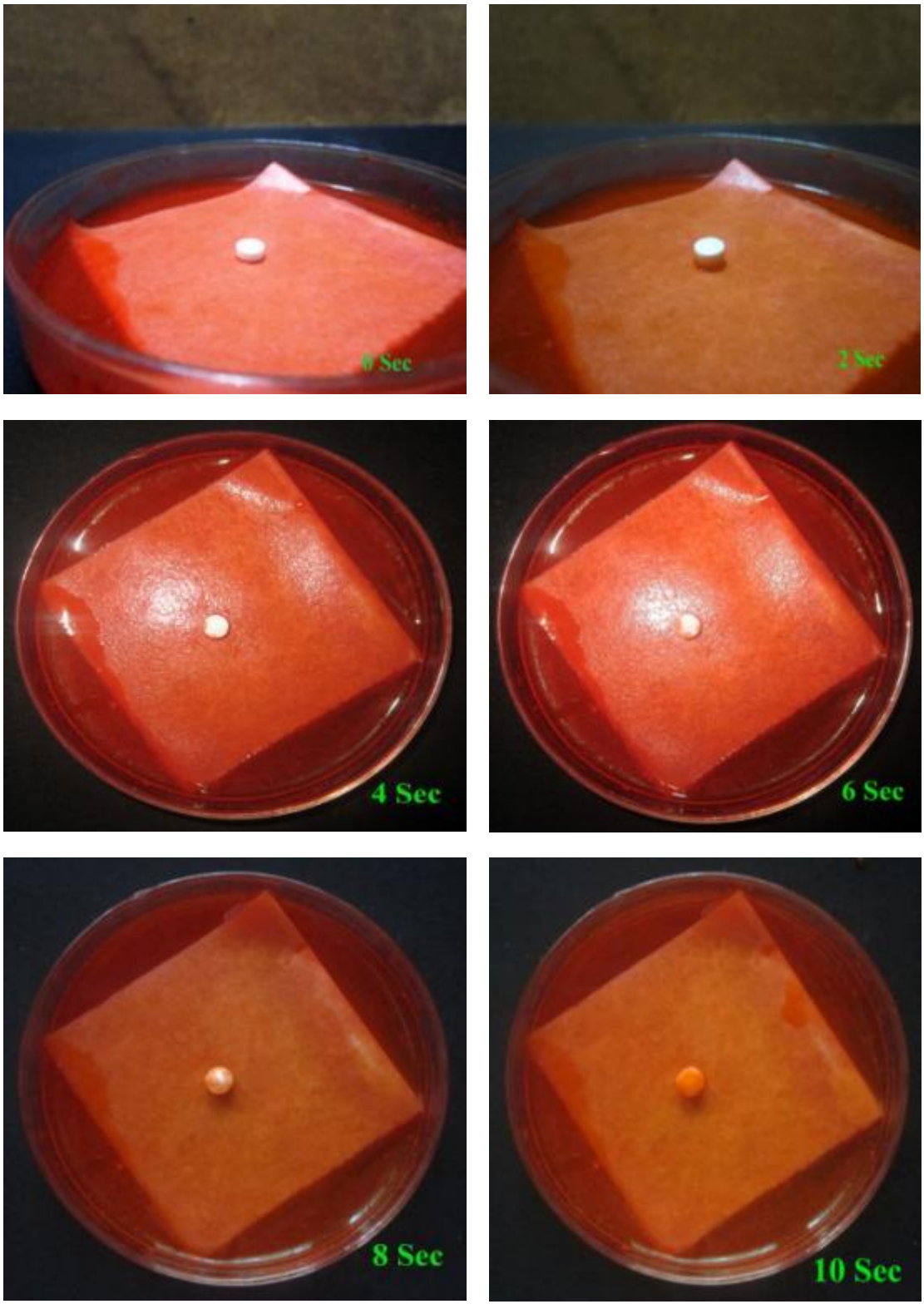


Figure 7: Wetting time for fast dissolving tablet (F27)

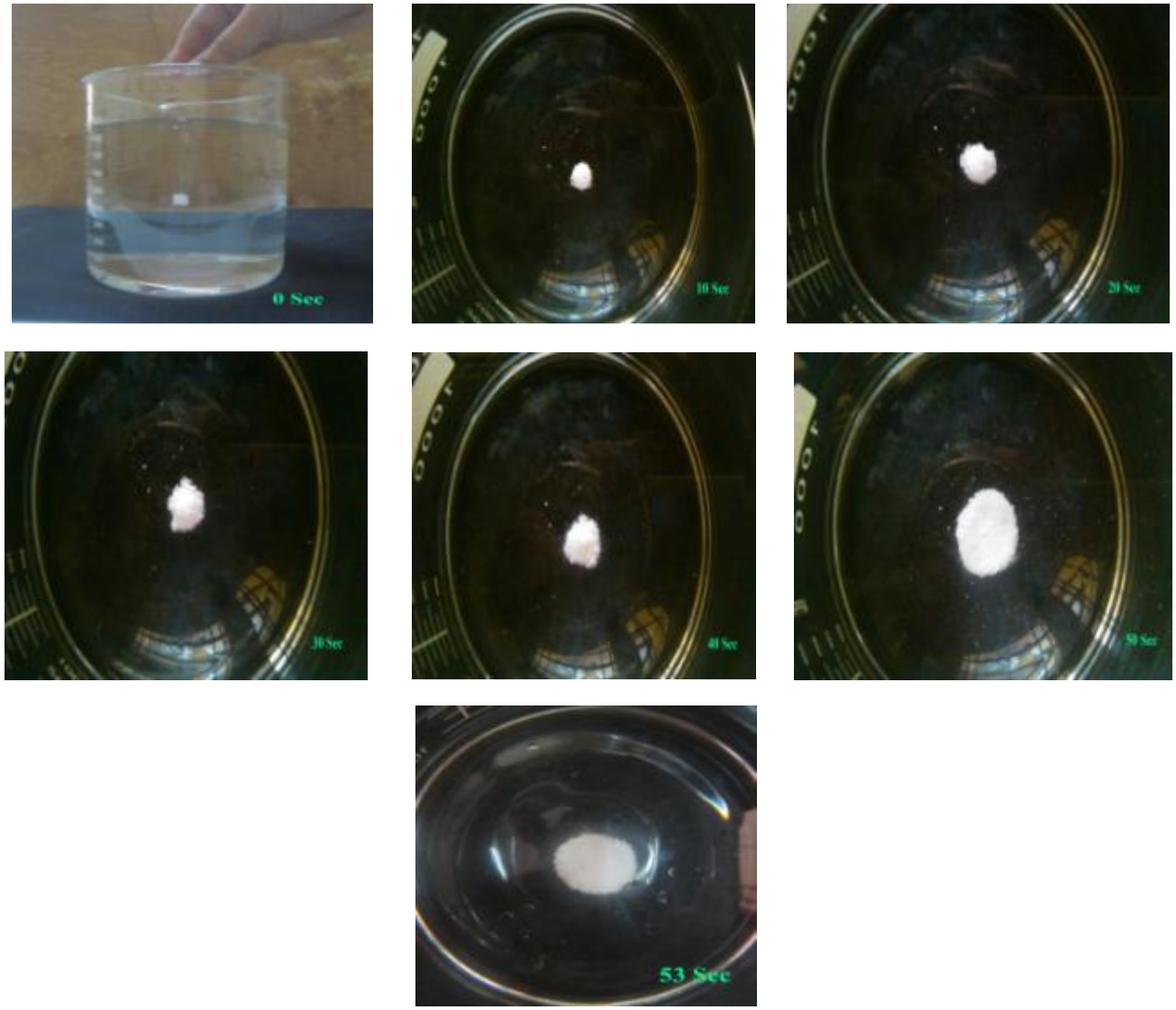


Figure 8: Disintegration time for fast dissolving tablet (F27)

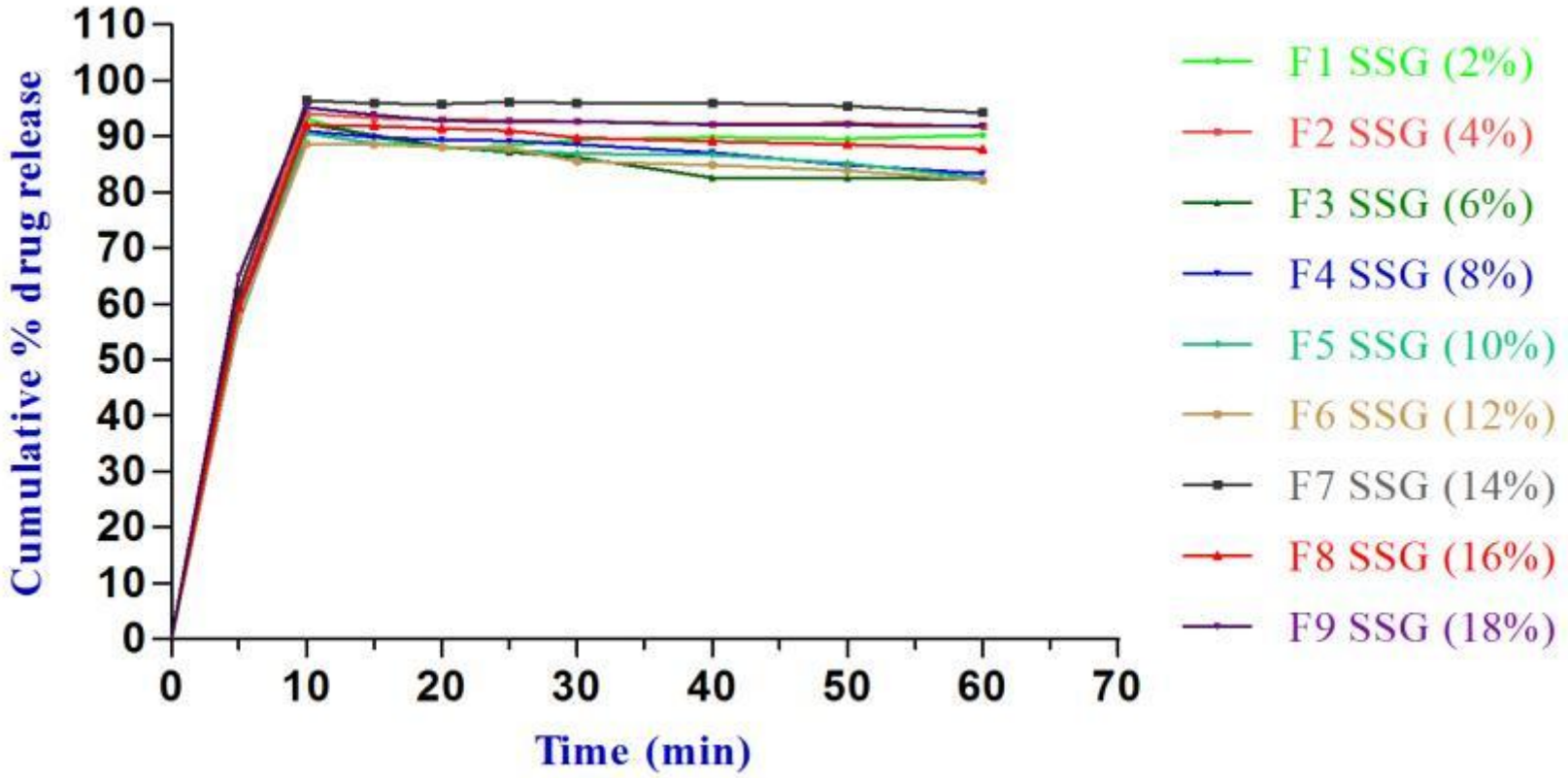


Figure 9a: Comparison of *Invitro* release profile of Torsemide containing different percentage of Sodium Starch Glycolate

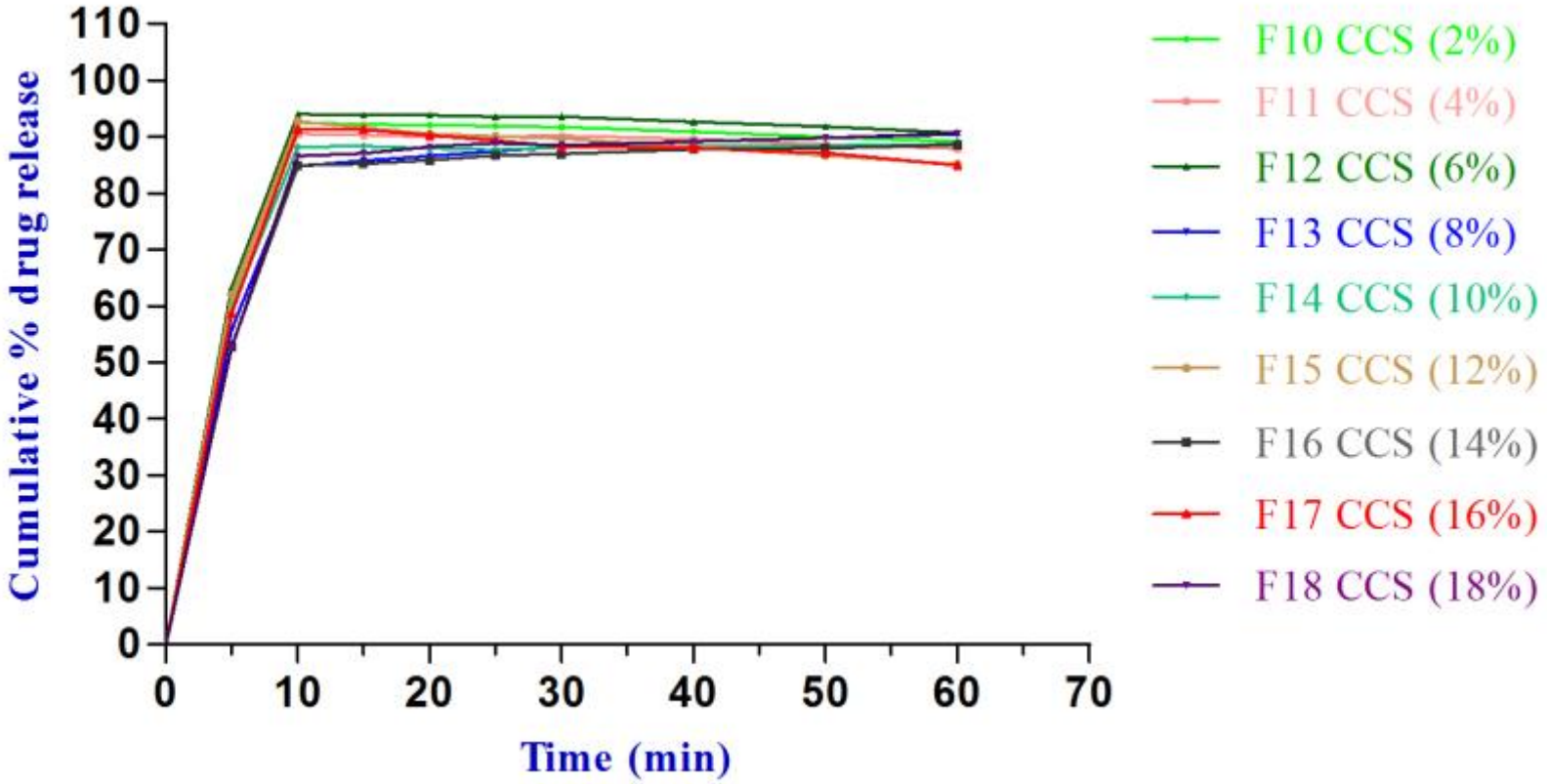


Figure 9b: Comparison of *Invitro* release profile of Torsemide containing different percentage of Croscarmellose Sodium

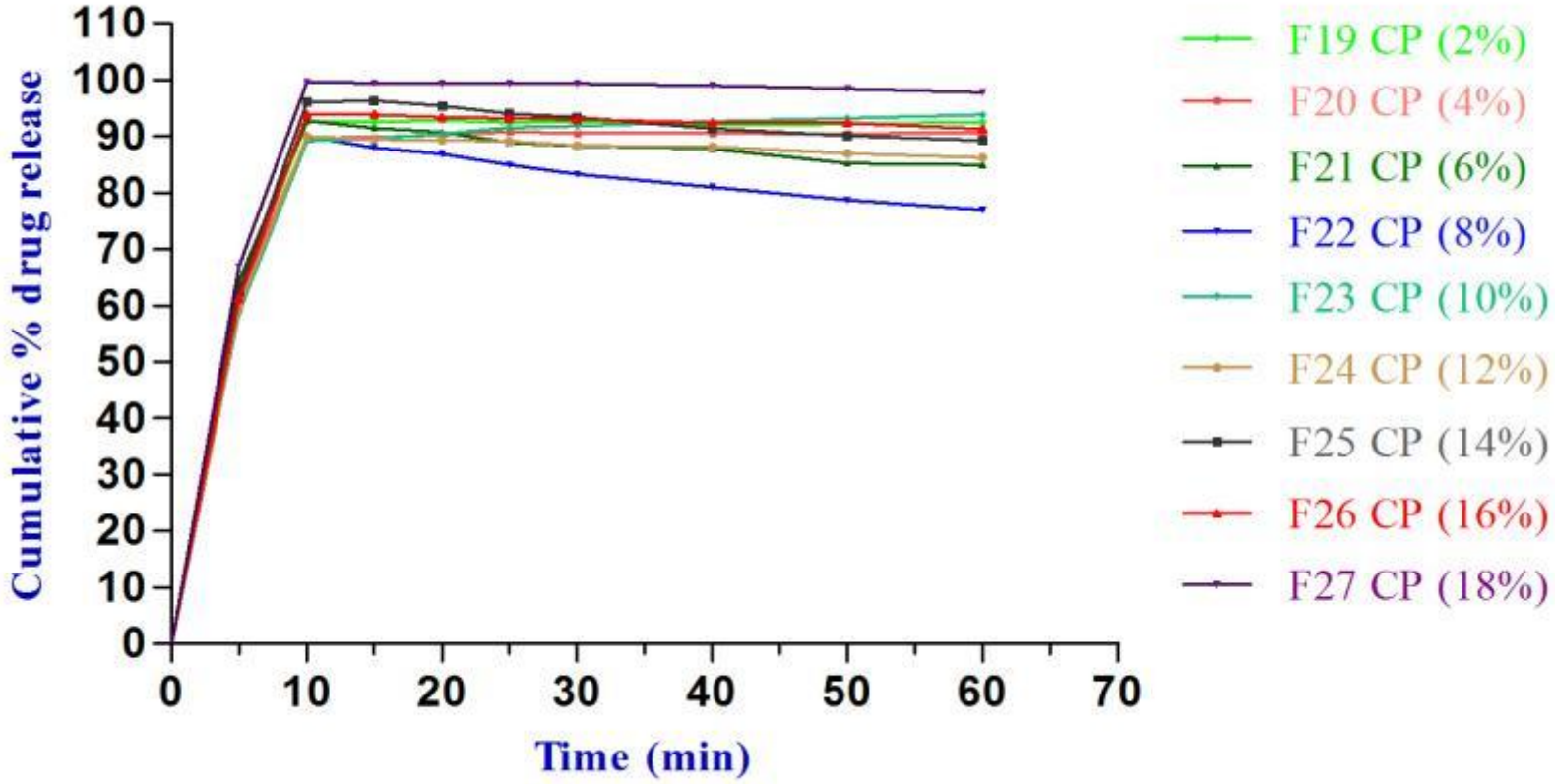


Figure 9c: Comparison of *Invitro* release profile of Torsemide containing different percentage of Crospovidone

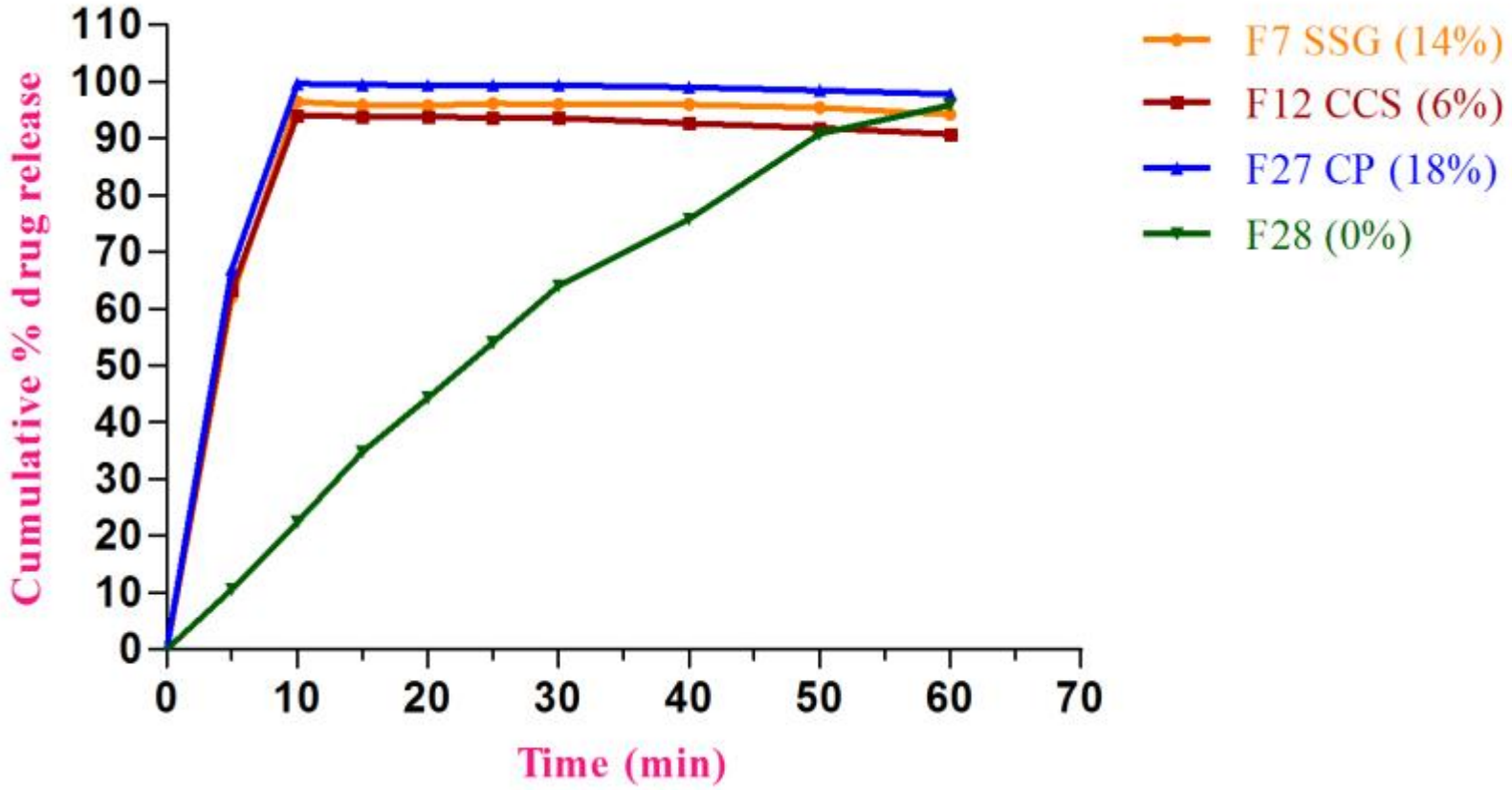


Figure 9d: Comparison of *invitro* release profile of Torsemide containing different super disintegrants and without super disintegrants

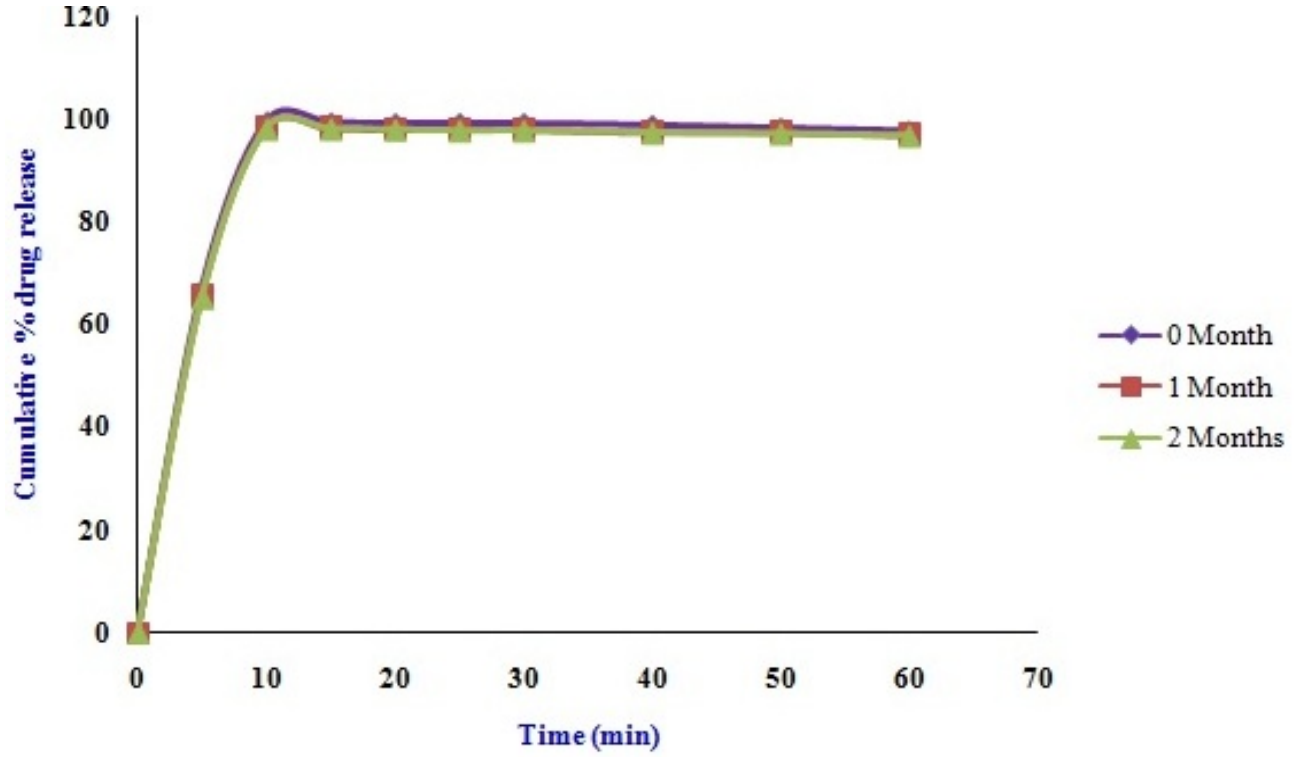


Figure 10: Comparison of *in vitro* dissolution profile (F27) of 0 month, 1 month and 2months (stored at 40^{o} C±2^{o} C and RH 75 %±5%)

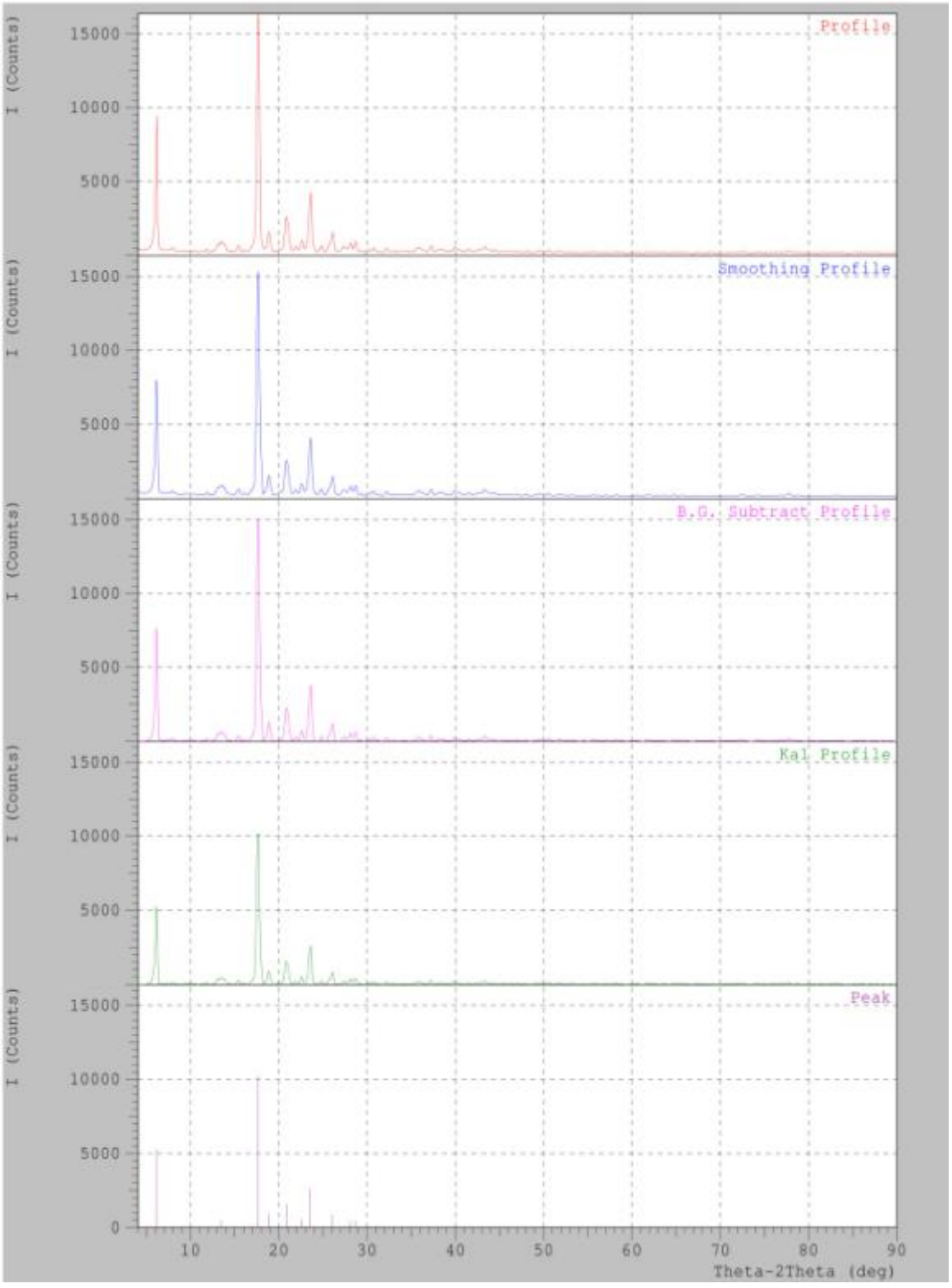


Figure 11a: Powder X-ray diffraction studies for Torsemide

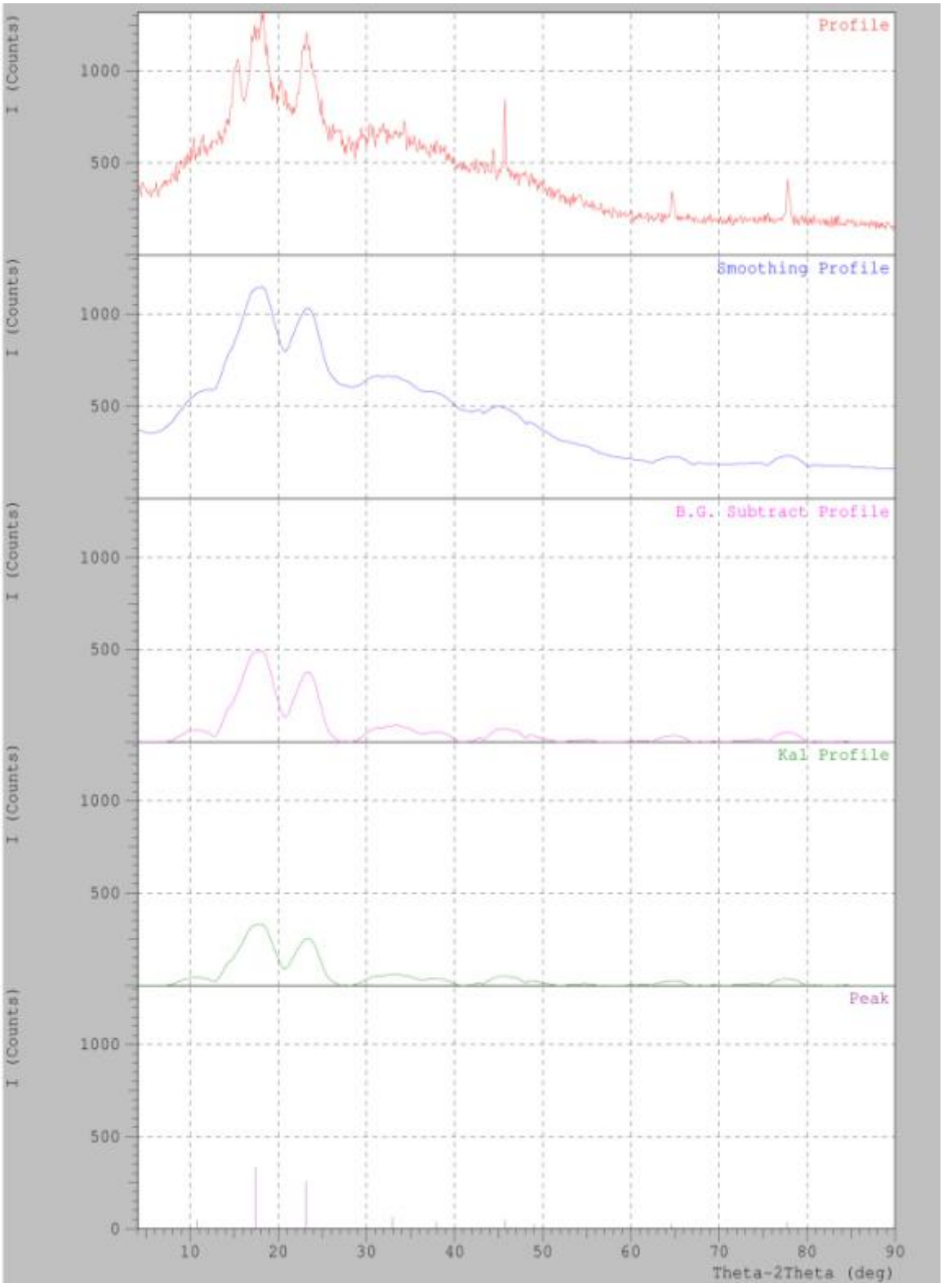


Figure 11b: Powder X-ray diffraction studies for sodium starch glycolate

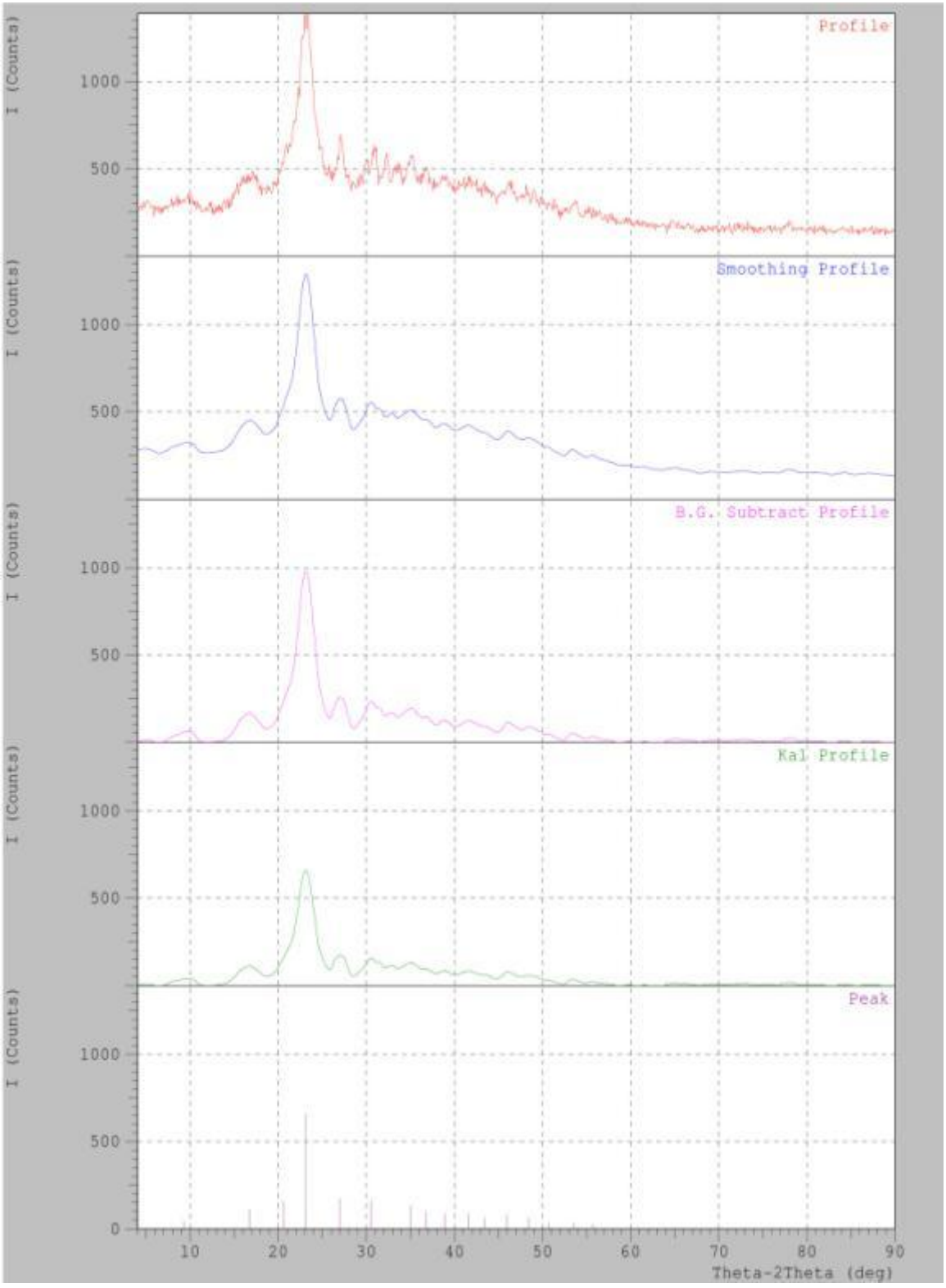


Figure 11c: Powder X-ray diffraction studies for croscarmellose sodium

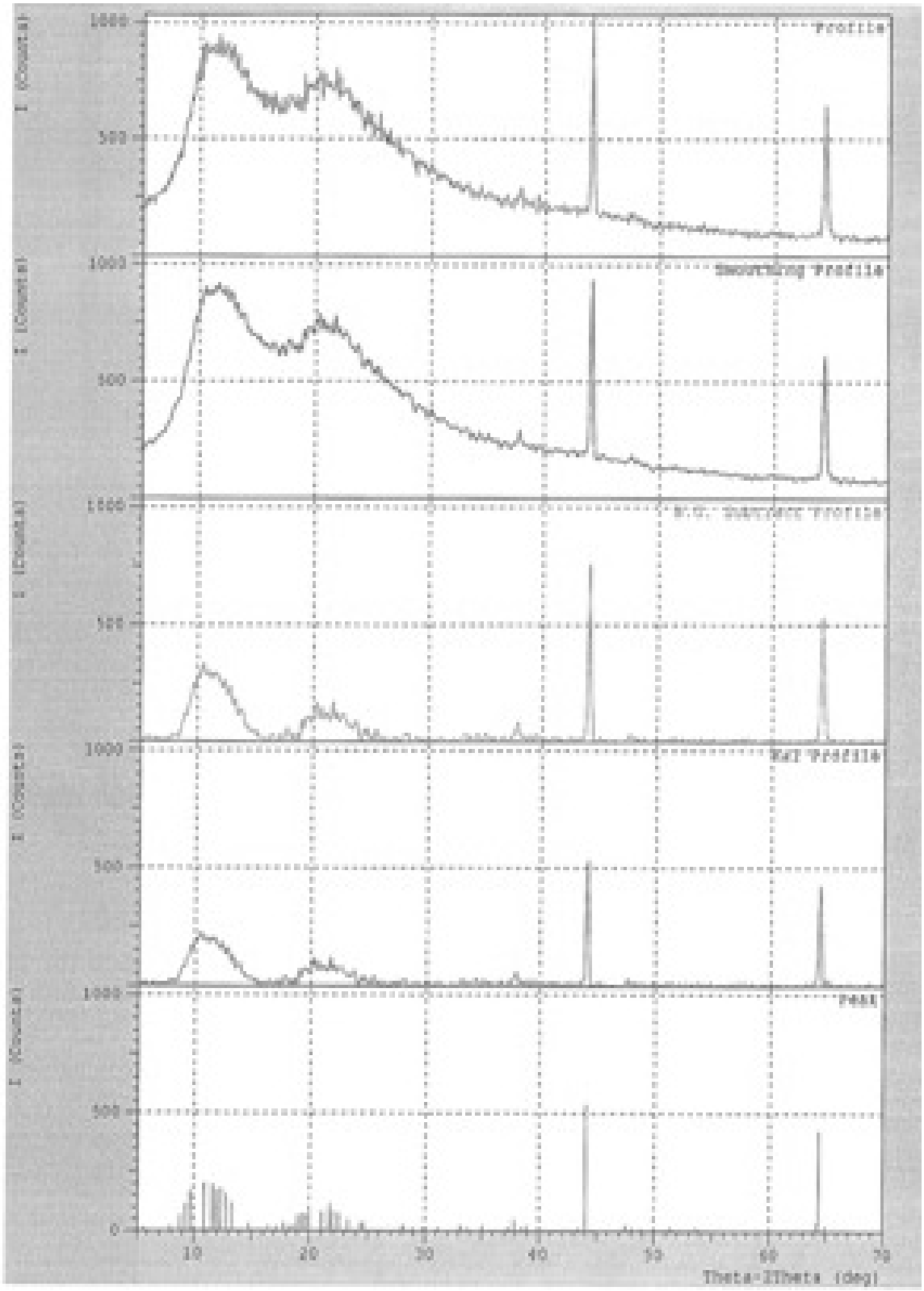


Figure 11d: Powder X-ray diffraction studies for crospovidone

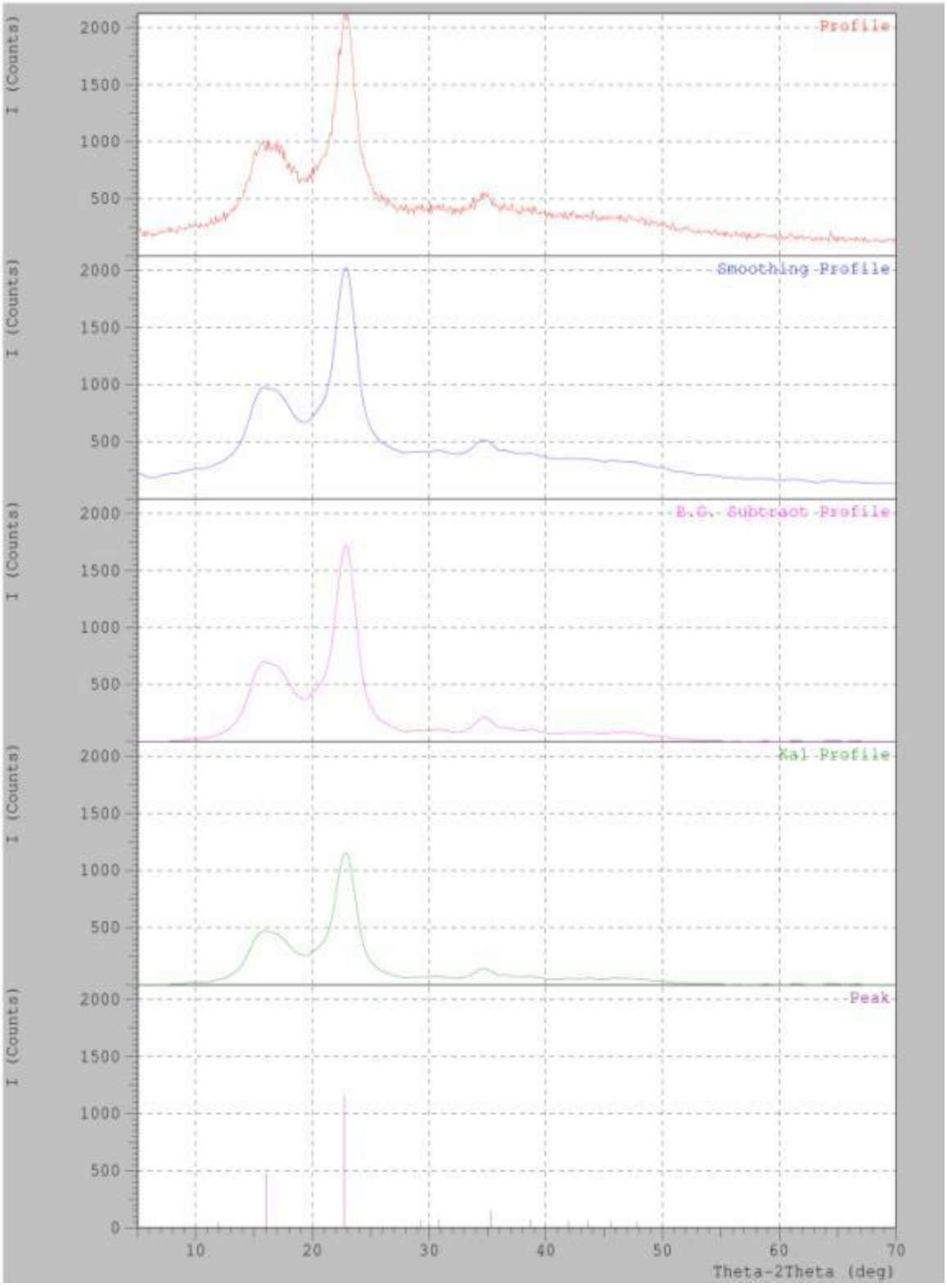


Figure 11e: Powder X-ray diffraction studies for microcrystalline cellulose

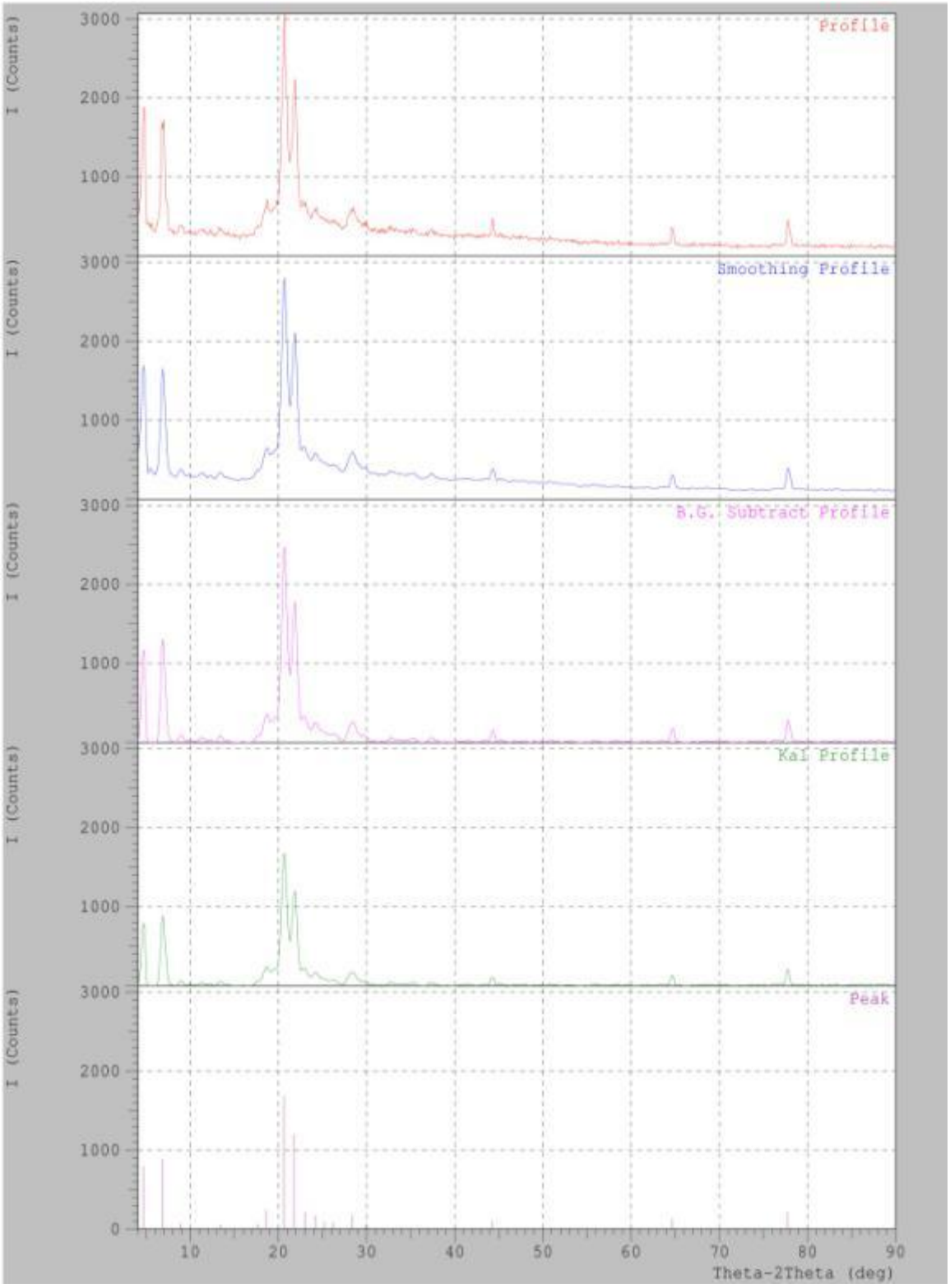


Figure 11f: Powder X-ray diffraction studies for sodium lauryl sulphate

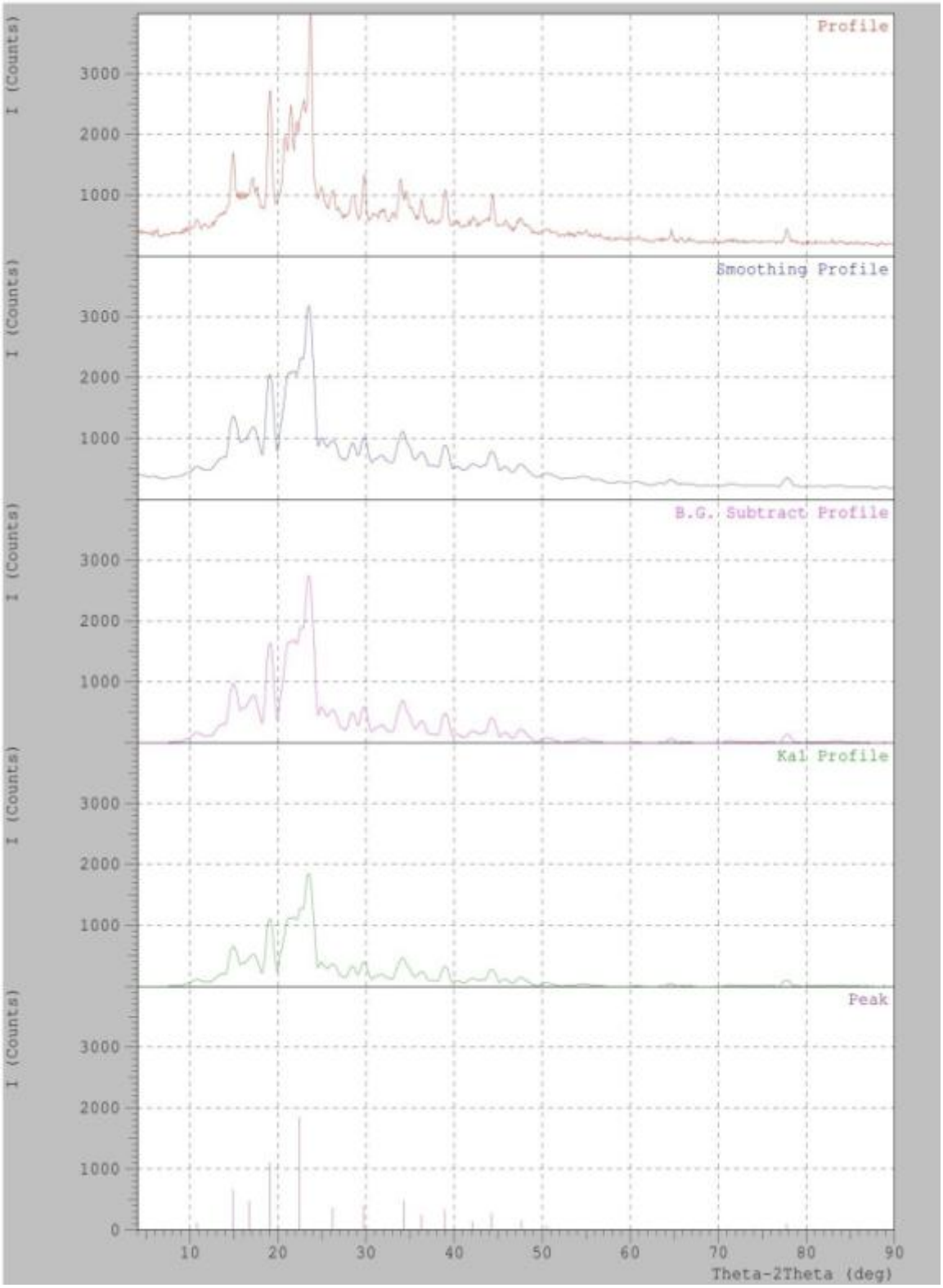


Figure 11g: Powder X-ray diffraction studies for Best formulation

CHAPTER X

SUMMARY AND CONCLUSION

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SUMMARY AND CONCLUSION

- The purpose of the study was to formulate and evaluate Fast Dissolving Tablets of Torsemide.
- The results of Fourier Transmission Infra-Red spectroscopy confirm that both drug and excipients are compatible with each other and are devoid of interactions.
- The results of precompression studies like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio reveals that the prepared powder blends of all formulations possess good flow properties.
- The tablets were prepared by direct compression method using super disintegrants like Sodium starch glycolate (F1 to F9), Croscarmallose sodium (F10 to F18) Crospovidone (F19 to F27) and without superdisintegrant (F28) in different concentrations of 2%,4%,6%,8%,10%,12%,14%,16%,18%. Mannitol is used as both binder and sweetener, sodium saccharin for additional taste masking and microcrystalline cellulose as diluent. The tablets obtained were of uniform shape and size.
- The prepared tablets were subjected to post compression evaluations and the results indicate that the hardness, thickness and diameters of all the tablets are uniform, which ensures that all the tablets were of uniform size and shape with good resistance against mech anical damage.
- The tablets of all formulations contains uniform amount of drug, which ensures content uniformity for tablets of all formulations.
- The tablets were within the limits of weight variation test, which in turn indicate uniform distribution of contents of the powder blends of each formulations.

- The friability of all the tablets was found to be < 1%, which indicates the good mechanical resistance.
- The tablets of all formulations were found to have minimum wetting time and maximum water absorption ratio which is the desired characteristic of fast dissolving tablets, which enables faster disintegration of tablets.
- The disintegration time of all tablets were found to be less than three minutes, which ensures faster disintegration except formulations (F28).
- The tablets of all the formulations were found to release more than 80% in 10 minutes, which is the desired quality of fast dissolving tablets that helps in faster absorption of the drug and quick onset of therapeutic effect except for formulations (F28). The dissolution pattern of various disintegrants used in the formulations was found to be in the order of Crospovidone > Sodium starch glycolate > Croscarmallose sodium.
- The DSC thermogram of Torsemide and final formulation, the sharp endothermic peak of pure drug appeared at 167.97^{o}C, whereas final formulation appeared at 168.31^{o}C, which indicates that there was no interaction between drug and excipients.
- The results of the powder X- ray diffraction studies proved that the crystallinity of pure drug was remarkably reduced in the best formulation.
- The selected formulation was found to be stable under the storage condition.

CONCLUSION

In present study, the fast dissolving tablet of torsemide, an anti-hypertensive drug was formulated with an objective to improve patient compliance and achieve rapid onset of action. Three different super disintegrants sodium starch glycolate, croscarmellose sodium and crospovidone were used in formulations. Formulation F27 containing 18% crospovidone has shown the better results for disintegration time of 53 seconds. *In-vitro* dissolution study showed 99.62% of drug release at the end of 10 minutes. The overall results shows F27 formulation was excellent. Stability study shows that there was no significant change in the selected formulation. Thus Crospovidone can be successfully used in the formulation of fast dissolving tablets.

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